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Myxedema: Record of an Autopsied Case with Special Emphasis upon Lesions of Muscles

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CONSIDERING the widespread interest in myxedema, the general pathological picture has been little understood. In the report on myxedema published by the London Clinical Society in 1888, a series of 20 autopsies was recorded (1). The report was chiefly concerned with the structural changes in the thyroid gland itself and in the pathology of skin and subcutaneous tissues. It was remarked, however, that interstitial changes in the internal organs were not infrequent. Especially emphasized were features closely resembling an interstitial nephritis which the committee was unwilling to regard as a consequence of hypothyroidism. The heart, examined in 9 of the 20 cases, was considered abnormal in only 2, one of which exhibited an early stage of interstitial myocarditis and the other a comparatively advanced stage of the same process. Some thickening of the adventitia of arterioles was also noted.

Since 1891, when Murray discovered that myxedema could be cured by the use of thyroid, autopsies have been infrequent and many of those which have been reported have failed to mention the state of all the organs. Gradually, however, certain features have been established while others still remain quite obscure. In a few cases which in retrospect may be regarded as secondary hypothyroidism, the pituitary gland has been entirely destroyed. In others it has appeared normal or has exhibited minor changes, the significance of which is not now interpretable. Perhaps the most significant feature is that in some cases of long-standing, untreated myxedema the pituitary may appear quite normal. Changes in other endocrine glands are not remarkable.

In other tissues, however, the consequences of myxedema may be more evident. In some advanced cases the heart has become dilated and the cardiac musculature has appeared to be hypertrophied. Microscopically, the muscle has exhibited fibrosis with swelling of muscle cells and vacuolization which may have accounted for the appearance of hypertrophy. Descriptions have varied but have included accounts of individual muscle cells in which the sarcoplasm was completely replaced by hydropic vacuoles. Some cells have been pale while others have been deeply stained with small pyknotic nuclei. Between the muscle cells there has been an accumulation of a faintly basophilic staining fluid, the chemical nature of which has not been determined. Similar changes have been noted by Webster and Cooke (2) in hypothyroid animals.

Skeletal muscles have exhibited similar changes in which the individual muscle fibers have been separated by faintly basophilic-staining edema fluid. The fibers have appeared frayed with imperfect striations.

Evidence of atherosclerosis is abundant. While this association in middle age and afterward might be coincidental, several cases of advanced atherosclerosis have been described in young adults.

Of extraordinary interest were the three cases of induced hypothyroidism with hypertension and spontaneous rupture of the aorta reported by Kountz and Hempelmann (3). In these patients in whom complete thyroidectomy had been performed 5, 31, and 5 months previous to the fatal accident, the aortas were found to exhibit a chromatotropic degeneration of the muscular coat of a type similar to the idiopathic cystic, medial necrosis of Erdheim (4) and of a degree entirely unexpected either with hypertension or in patients under the age of 40. These cases are important because they indicate the possibility of muscle changes in blood vessels similar to those which have been emphasized elsewhere in relation to the skeletal muscles and the heart. Observations on arteries in autopsied cases of myxedema have been notably incomplete except for attention focussed on the extent of atheromatous or intimal changes.

Study of the following case illustrated some points of clinical and pathological interest and afforded an opportunity of examining rather completely the lesions in a relatively large number of muscles in a case of long-standing myxedema.

CASE REPORT

G.T., a widow of 60, had enjoyed good health until the age of 48 when she was extensively burned by scalding water. It was during the three months' convalescence from this painful accident that her daughter first noted that she was dull, listless and disinterested. She slept most of the day and all of the night. Her appetite was poor and she was irritable when disturbed. Her face became puffy; her skin thick and rough; her hair coarse and sparse. Gradually all of her body hair and most of the hair of her head fell out. When she was 57 her husband died and following this she lost all interest in life. Although she continued to do some housework, her ankles swelled and she became dyspneic, following slight exertion. Nine months before her admission to the hospital she suffered a severe attack of diarrhea. With this she took to her bed and although the diarrhea was controlled, she did not get up again. She slept most of the time and was kept alive over long periods by forced feedings. Three months before she entered the hospital her abdomen began to swell and it was noted that slight injuries caused rather extensive subcutaneous hemorrhages.

Physical examination. At the time of admission she was lying flat in bed completely relaxed and displayed no interest in her surrounding. Responses to questions were slow and deliberate but not lacking in intelligence. Her voice was not abnormal. The skin over her entire body was extremely fine and beneath the paper-thin epidermis there were numerous old and recent hemorrhages. Over the extremities there was a marked loss of subcutaneous fat. The hair of her head was coarse and very scanty with large areas of alopecia and patches of seborrhoeic dermatitis. There was no hair in the axillae and pubic regions. Her face was pallid and moderately edematous. The eyes were sunken, the pupils were round, regular and equal, and reacted to light; the extra-ocular movements were not impaired; the sclerae were

clear with no evidence of jaundice. The conjunctivae were very pale. Hearing was not grossly impaired. All of her teeth were missing. The tongue was not particularly or abnormally red and its papillae were well preserved. The mucous membranes of the mouth were pale and moist. The pharynx was clear. The thyroid gland was not palpable. It was thought that the trachea was slightly deviated to the left but no masses could be felt in the neck. The chest was kyphotic and the diaphragms were slightly elevated. A few râles could be heard at the pulmonary bases. The heart was not enlarged to percussions. The rhythm was regular; the rate, normal; the sounds, distant. The brachial and radial arteries were thickened. The blood pressure was 130/80. The abdomen was enormously distended without sagging of the flanks. A fluid wave was easily demonstrated. No masses or organs were palpated. The pelvic examination was not abnormal and the rectal examination revealed external hemorrhoids. The scars of an old burn were apparent on the buttocks and lower abdomen. There was marked pitting edema in the dependent portions of the abdominal wall, in the back and in the lower extremities.

The evidences of a mild osteoarthritis were noted. Wasting and atrophy of the muscles of the upper extremities were evident. All muscular movements were slow and deliberate. Both deep and superficial reflexes were intact and no neurological abnormalities were discovered.

Laboratory data. RBC, 3,270,000; WBC, 8,350; Hgb., 65%; Schilling B-1, E-2, Stab-51, Lym-21, Mono-4, RBC normal in size and shape, moderate number of platelets. No parasites were seen. Urine—cloudy, acid, sp.gr. 1.024, no sugar, albumin 2+, numerous RBC per HPF, 15–20 WBC/HPF, no casts. Urine culture negative. N.P.N., 21 mg.%. Fasting blood sugar, 63 mg.%. Total protein, 4.6 gm.%; albumin, 2.1 gm.%; globulin, 2.5 gm.%. Kahn test was negative. Blood cholesterol was 120 mg.% and on two other occasions, 126 and 137 mg.%. Stool was semiliquid, brown, no ova or parasites; negative guaiac. BMR was minus 46%. An electrocardiogram showed very low voltage in all leads. A repeated urine showed an occasional RBC, 20–30 WBC, no casts, and albumin disappeared to only a faint trace. Twenty-four hour output revealed only 45 mg.% protein. Circulation time, using decholin was 15 seconds. Prothrombin time was 40 seconds, to control 45 seconds. Venous pressure was 85 mm. of water. At no time was there any occult blood in the stool. The serum calcium was 8.6 mg.%; phosphorus, 3.2 mg.%, alkaline phosphatase, 2 Bodanski units. Creatinine excretion was 1.4.

Treatment was instituted on the understanding that this was a case of extreme myxedema complicated by a high degree of undernutrition. Gradually increasing doses of thyroid caused elevation of the basal metabolic rate to −36%, −26%, −12% and finally after 6 weeks of treatment to −2%. The EKG revealed an increase in voltage in all leads. The blood cholesterol rose to 176 mg.%. Every effort was made to correct the undernutrition and to increase strength by repeated transfusions, the use of intravenous aminoacids, intramuscular liver therapy and parenteral vitamins. Plasma proteins rose to 5.8 gm.% with 2.8 gm.% albumin and 2.9 gm.% globulin. The red-cell count increased to 3,380,000 and hemoglobin to 11.3 gm. The peripheral edema varied from time to time but did not disappear. Fluid which accumulated in the pleural cavities was tapped and was found to have a total protein content of 1.2 mg.%. Various diuretics were given with only temporary good effect. Great difficulty was experienced in controlling the distention of the abdomen which was at times enormous and greatly interfered with breathing.

Until a week and one-half prior to her death she showed some evidence of improvement. At that time, however, her distention became much greater. Fluid accumulated in both the abdomen and pleural cavities. Peripheral edema was exaggerated, intercellular fluid, tapped from the dependent edema, contained 638 mg.% of total protein with 518 mg.% of albumin and 120 mg.% of globulin. At no time was there evidence of cardiac incompetence or peripheral circulatory failure. The blood pressure remained normal until the time of her death. She became, however, more and more unresponsive and finally died in coma.

AUTOPSY

The autopsy was performed one hour and 55 minutes post mortem.

Gross examination. The body weighed 62 kilograms and measured 167 centimeters in length. The head was normal in size and shape, but there was only a small amount of gray hair on the scalp. The hair line anteriorly was at the level of the coronal suture. The face, neck, chest, and upper extremities were markedly

emaciated, while the abdomen and lower portions of the body were edematous. The eyes were sunken. The conjunctivae were pale. There were no teeth and upper and lower dental plates were present. The thyroid was not palpable and there were no enlarged lymph nodes in the neck. The bony landmarks of the chest were prominent. The breasts were small, atrophic, and contained no nodules. The abdomen was protuberant and tympanitic; there were many white striae present over the lower and lateral portions of the abdomen. The external genitalia were markedly edematous and the pubic hair was absent. The lower extremities were markedly edematous but were otherwise normal. The upper extremities were thin and the skin over the upper portion of the body was loose and dry. The muscles of the arms were atrophic.

The peritoneal cavity contained 2800 cc. of yellow serous fluid. There were a few firm fibrous adhesions between the gall bladder, the duodenum, and the hepatic flexure of the colon. The peritoneum was otherwise smooth and glistening. The sigmoid colon was enormously enlarged, beginning at a point 2 centimeters above the pelvic brim and extending 4 centimeters below the pelvic brim. This portion of the intestine appeared to be greatly elongated and had a maximum diameter of 16 centimeters. The length of the distended portion measured 29 centimeters.

Each pleural cavity contained 400 cc. of clear, yellow fluid. The pleura was smooth and glistening and there were no adhesions.

The pericardial cavity contained 100 cc. of clear, yellow fluid. The pericardium was normal.

The thymus was indistinguishable in the fat of the superior mediastinum. In the upper portion of the mediastinum lying over the arch of the aorta and between the sternal junctions of the first ribs, there was a thick-walled, round, only moderately firm cyst, 2 centimeters in diameter. On section this cyst contained a small amount of greasy, yellow, thick fluid; the wall was 7 millimeters in thickness and the cyst was lined by a smooth white surface.

The thyroid gland weighed 7 grams and was difficult to separate from the surrounding tissue. It was firm, white, and was roughened by small tags of fibrous tissue adherent to the surface. On section the cut surface of each lobe was white and smooth except for four or five small brown nodules in each lobe. The largest was 2 millimeters in diameter and most of them were less than 1 millimeter in diameter. The left lobe measured $35 \times 15 \times 10$ millimeters and the right $25 \times 8 \times 12$ millimeters.

The heart weighed 220 grams. The tricuspid, pulmonic, mitral and aortic valvular rings were 111, 62, 83 and 66 millimeters in circumference respectively. The thickness of the right ventricular wall was 4 millimeters and that of the left ventricular wall was 18 millimeters. There was slight thickening of the endocardium beneath the tricuspid valve. The tricuspid valve was thickened at the periphery where the chordae tendineae insert, but this was not marked. The mitral valve was similarly thickened at the insertion of the chordea tendineae and there was slight fibrosis on the tip of the papillary muscle. There was a firm fibrous adhesion between the posterior and right cusps of the aortic valve which in no way prevented the cusps from closing. There was a thin, yellow, 3×4 millimeter plaque in the aortic leaflet of the mitral valve.

The aorta and the coronary, renal and cerebral arteries showed a moderate degree of thickening of the intima, in the form of round, yellow, slightly raised plaques. In no area did these plaques obstruct the lumen of the vessel.

The lungs together weighed 890 grams. The pleural surfaces were smooth and glistening and beneath the pleura were many fine lines of black pigment. The periphery of each upper lobe was white and there was increased crepitus to palpation. The lower lobe of each lung was gray, firm, and non-crepitant. On section the upper lobes exuded a small amount of frothy, pink fluid. The lower lobes were firm in consistency and exuded dark red fluid on pressure. There was a recent thrombus in the branch of the pulmonary artery to the lower lobe of the right lung. No other thrombi were found in the pulmonary vessels. There were small, fibrous scars at the apices of the lungs. These were stellate and the largest was 5 millimeters in diameter.

The liver weighed 1600 grams. The capsule was smooth except over the anterior surface opposite the gall bladder fossa, where there was slight, fibrous thickening. The edges were sharp and the surface was light brown. On section the lobular markings were indistinct and the cut surface was brown, mottled with yellow. The intrahepatic bile ducts were not dilated. The cut edges averted slightly.

The gall bladder contained 25 cc. of cloudy, yellow bile. The wall of the gall bladder was 5 millimeters in thickness; and although the mucosal surface had the usual mosaic, there was a 5 millimeter scar in the anterior wall. The cystic ducts and extrahepatic bile ducts were grossly normal.

The spleen weighed 125 grams. The capsule was smooth, slate blue, and contained several small areas of white fibrous thickening. On cut section the surface was level with the cut edges. The dark purple pulp was firm and the trabeculae were prominent. The follicles were distinguishable.

The pancreas weighed 90 grams and was yellowish white in color. The surface had the usual lobulated appearance. Cut section revealed no abnormal change.

The adrenals together weighed 12 grams and were externally normal in size, shape, consistency, and color. On cut section the cortex was thinner than usual.

The right kidney weighed 140 grams and the left kidney weighed 150 grams. On cut section the cortex and medulla were distinct. The capsule stripped with moderate difficulty, leaving a light brown, finely granular surface. The pelvis of the left kidney was slightly dilated but the mucosa was normal. The pelvis of the right kidney was moderately dilated, and the lumen of the upper 2 centimeters of the ureter was similarly slightly enlarged. The left ureter was slightly

dilated and its wall was slightly thickened. The mucosa of each was normal.

The bladder contained 200 cc. of cloudy urine. In the orifice of the right ureter was a 1×1 millimeter yellow, rough calculus. There were no other calculi present in the urinary tract. The mucosa of the bladder was smooth and white.

The ovaries together weighed 4 grams. They were small, white, and fibrous. Section revealed no follicles. The fallopian tubes were normal. The uterus was atrophic and slightly more firm than usual. From the left side of the cervical canal hung a small, soft polyp measuring 2×2×7 millimeters; this projected through the external os. The endometrial surface of the uterus was pink and smooth.

The esophagus, stomach, duodenum and remainder of the small intestine were normal in appearance. The ascending and transverse portions of the colon contained 1900 grams of soft yellow feces; the diameter and the mucosa of the large intestine were normal to a level 2 centimeters above the pelvic brim. At this point the sigmoid became enormously enlarged. This portion of the intestine appeared to be greatly elongated and had a diameter of 16 centimeters. The wall was 3 mm. thick and appeared edematous. The length of the distended portion was 29 centimeters. There was no obstruction either at the upper or lower end of the dilatation and no thickening of the wall.

The cranial cavity was anatomically normal except for the pituitary fossa. The posterior wall was much thinner than usual, there being only the two layers of dura with no bone between in some areas. The brain weighed 1470 grams.

The pituitary gland weighed 950 milligrams. The anterior lobe partially encircled the posterior lobe and was moderately enlarged laterally. On section no change was seen in the usual structure except that of size.

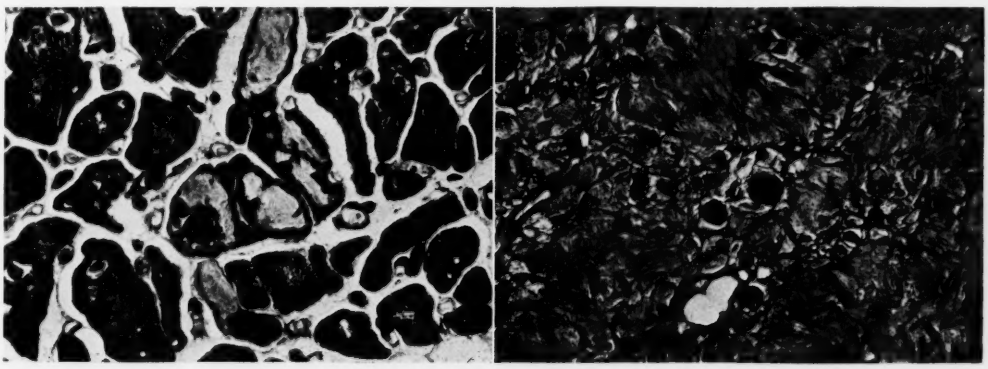

FIG. 1 (Left) Heart Muscle. A high-power section of the heart muscle near the endocardium of the right ventricle, showing the vacuolated muscle cells which contain a light blue-staining homogeneous material. This is described in Henke-Lubarsch as typical of myxedema. Hematoxylin and eosin stain. High power.

FIG. 2. (Right) Section through the muscle layer of the distended portion of the sigmoid colon. Notice the degeneration of the muscle cells similar to that seen in the heart. Henke-Lubarsch does not describe this. Heidenhain stain. High power with a blue filter.

MICROSCOPIC EXAMINATION

Heart. There was slight proliferation in the subendocardial tissue of the ventricular surface of the base of the mitral valve and a small area of calcification was present in the leaflet. The subendocardial fat cells were collapsed and wholly or partially filled with fine eosinophilic granules. The intercellular spaces also contained this material. A section through a small area which appeared grossly to be a scar in the surface of the left ventricle revealed a small, partially hyalinized, fibrous plaque in the epicardium overlying an area of atrophic muscle cells embedded in a focus of fibrous tissue. Several sections taken from various areas in the ventricles all showed replacement of the central part of many heart-muscle cells by a clear or slightly granular mass of basophilic material. The change was not present in every cell, or in adjacent cells, but was irregularly scattered throughout the myocardium. These basophilic areas usually filled from two-thirds to nine-tenths of the cell on cross section and involved only the sarcoplasm. The sarcolemma was unaffected. In these areas the muscle cells were swollen and were from one and a half to two times normal size. In longitudinal section the basophilic foci varied in length but averaged sixty microns. With Heidenhain's aniline blue stain, these foci appeared lighter blue than the surrounding tissue, and with cresyl violet they exhibited varying shades of purple.[1]

Aorta. Throughout the medial part of the wall of the aorta there was loss of smooth muscle cells and collagen. The spaces thus formed were filled with a homogeneous basophilic material resembling that seen

[1] The heart muscle and other muscles were studied from routine autopsy sections and were fixed in Helly's fluid or 10% formalin. The stains used were hematoxylin-eosin, Heidenhain's aniline blue, Masson's trichrome, and cresyl violet. The techniques were those described by Mallory.

in the vacuolated heart-muscle cells. In a few places there were small cysts filled with this material. The internal and external thirds of the aortic wall were only slightly affected and contained no cysts. The adventitia and intima were normal.

Striated muscle. In sections from the right pectoral muscle there was replacement of the central parts of some of the fibers by granular or homogeneous basophilic material, identical with that in the cardiac muscle cells. Only a few cells were affected but in these there was destruction of the entire sarcoplasm in areas up to one hundred microns in length. Other muscle cells showed a loss of cross striations and had

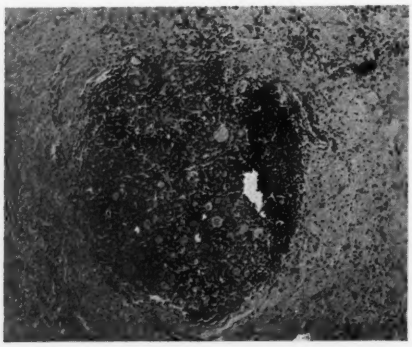

FIG. 3. A low-power view of a section from the right lobe of the thyroid. A nodule of thyroid tissue in the midst of the large amount of fibrous tissue is one of three or four in the entire lobe. Note the lymphocytic infiltration and the solid cords of cells of thyroid epithelial origin in the nodule.

a hyaline appearance like that seen in Zenker's hyaline degeneration.

Skin. There was disturbance in keratinization with slight hyperkeratosis. In the granular layer there was ballooning degeneration of scattered epithelial cells. The surface layers were slightly eroded in some foci. Just beneath the epidermis there was dilatation of the capillaries. The dermis was infiltrated with lymphocytes, a few plasma cells, and occasional polymorphonuclear neutrophils. Edematous collagen was noticeable in the lamina propria.

Lung. There was slight but definite fibrous thickening of the alveolar walls. One part of the section showed marked thinning of the alveolar walls with coalescence of the alveoli to form relatively large, clear spaces. Focally there was a slight perivascular and peribronchial fibrosis. Large mononuclear phagocytes were rarely present in the alveoli but small groups were present in the peribronchial connective tissue.

Liver. One section revealed a slight increase in the fibrous tissue of the central vein and periportal areas. The sinusoidal walls were separated from the liver cells by a space filled with minute eosinophilic granules. This change was present in nearly every lobule. In a second section the cords of the central zone were disrupted, atrophic or absent. The nuclei of some of the few remaining liver cells were pyknotic. Numerous large mononuclear phagocytes were present and contained black or bluish-green pigment granules. There were many lymphocytes and a few polymorphonuclear neutrophils scattered through the central zone and with many sinusoids were collapsed while others were filled with erythrocytes. The periportal areas contained a few small, tortuous bile-ducts but there was only a slight connective tissue increase.

Gall bladder. The mucosa of the gall bladder was normal. In the smooth muscle of the wall there were occasional foci of blue, homogeneous material similar to that in the heart and aorta. The muscle cells containing these were slightly larger than the surrounding cells. A more pronounced change was seen in the walls of two small arteries in the section. In them there were areas of basophilic homogeneous material which in some foci were large enough to be considered small cysts. The intima of these vessels was normal and the change was present in the media. It was identical with the change in the aorta.

Spleen. The Malphigian bodies were prominent and consisted primarily of the large, lymphocytic-type cells. Throughout the pulp the sinusoids were engorged with erythrocytes which in some areas had lost their staining characteristics.

Pancreas. There was little fat present in the pancreas, but all the cells showed the same change as was seen in the fat of the heart. The parenchyma and ducts were normal.

Kidney. In many glomeruli the basement membrane was irregularly thickened and in some there was slight hyalinization of the tuft. Many showed a slight hyperplasia of the epithelial cells lining the tuft and Bowman's membrane. In some the subcapsular space contained basophilic debris. Scattered throughout the cortex were occasional, small, stellate, fibrous scars. The tubules and pelvis were essentially normal. Some of the small arterioles showed moderate medial thickening.

Urinary bladder. The epithelial surface was denuded of cells except in a few areas. There were numerous dilated capillaries in the submucosa. Throughout the smooth muscle bundles of the wall were small basophilic cysts or vacuoles that were most easily seen in the longitudinal section. These were similar in staining characteristics to the basophilic areas in the walls of the aorta and blood vessels.

Sigmoid. In a section through the wall of the dilated sigmoid, most of the epithelial cells were normal but there was an excess of mucus-filled, goblet cells. The submucosa contained numerous lymphocytes, plasma cells and large mononuclear phagocytes. In the muscle layer many of the cells had indistinct cytoplasmic outlines and seemed swollen. Heidenhain's stain showed many to have a central vacuole laden with basophilic homogeneous material similar to the vacuoles seen in the heart. The fat showed the same change as was present elsewhere in the body. A section through the colon proximal to the dilated segment showed less swelling of the muscle cells in general.

There were, however, a considerable number of muscle cells containing basophilic cytoplasmic vacuoles similar to those in the dilated segment.

Uterus. The surface cells of the endometrium were absent but in the deeper layers there were occasional small groups of dilated glands lined by low columnar epithelium. In the smooth muscle of the uterine wall there were occasional small foci of basophilic granular or homogeneous material similar to that seen elsewhere. In the walls of some of the uterine arteries there were large amounts of this material. In a few there was almost complete destruction of the walls with formation of large spaces filled with it.

Thyroid. A cross section of one lobe of the thyroid revealed almost total replacement of the acini by dense fibrous tissue. There were occasional acinic structures seen singly or in small groups which were lined by epithelium. These had no lumen. The larger ones had a peripheral zone of small polygonal or cuboidal cells with acidophilic cytoplasm and small dark nuclei. Centrally the cells were also polygonal but were larger and the nucleus stained lighter and contained a small nucleolus. These acinic structures were surrounded peripherally by a thin zone of lymphocytes and occasional scattered plasma cells. A few small nodules of recognizable thyroid tissue were present but even in these, lining cells were taller than usual and a few acini contained desquamated cells in the lumen. The acini were variable in size, shape and amount of contained colloid and a few were normal. Around each of these nodules of tissue were lymphocytes, scattered and in small groups. One small nodule was composed of papillary septa lined by low cuboidal cells and projecting into the lumens of the acini. In none of the acini did the epithelium have a basement membrane. The arterioles throughout the section showed medial thickening.

Pituitary. There was a slight increase in the number of basophilic cells in the anterior lobe with a few strands invading the posterior lobe. In none of these cells was Crookes' hyaline change present. In the periphery of the anterior lobe was a focal area of fibrosis which was small.

Bronchogenic cyst of upper mediastinum. The cyst was lined with pseudostratified, ciliated, columnar epithelium surrounded by a thick zone of dense fibrous tissue. There was a peripheral zone of fat which showed the same changes seen in the fat of the heart. In the fat and fibrous tissue were small round or linear structures composed of small polyhedral or fusiform cells. These resembled epithelial cells and had a scant acidophilic cytoplasm and a small, dark nucleus. These surrounded blood vessels and near them were a few, large, mononuclear phagoctyes.

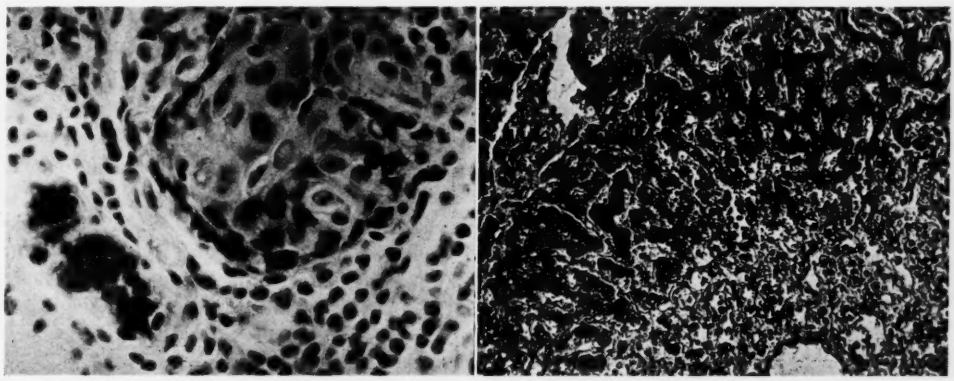

FIG. 4. (Left) A high-power view of one of the nodules of thyroid tissue, from the same lobe as fig. 3, containing solid cords of squamous-like epithelial cells. Note the smaller solid cords of the same cells. Both these sections were stained with hematoxylin and eosin.

FIG. 5. (Right) Liver. There is a central necrosis present in which many erythrocytes are seen in the central area, serious hepatitis of the periphery of the lobule, and a few polymorphonuclear neutrophils in the central zone.

DISCUSSION

Certain clinical features are worthy of comment. It seems probable that the hypothyroidism in this patient had existed for at least 12 years. Some of the characteristics of very advanced myxedema were illustrated, among them the tendency to accumulate large amounts of fluid in the pleural, peritoneal and pericardial sacs and the low voltage of the electrocardiograms. It is notable, however, that in spite of the long duration of the illness the heart showed no evidence of dilatation and that the circulation time was only moderately prolonged and that no significant circulatory influence on the accumulation of fluid could be detected. The basal metabolic rate of minus

46 was unusually low and was attributed to the combined effects of undernutrition and hypothyroidism. Quite remarkable were the low cholesterol values which were checked and rechecked with the greatest care. Emaciation, atrophy and low serum proteins were testimony to profound undernutrition. It cannot be stated to what extent the entirely unexpected value for cholesterol might have been due to this factor. In light of the general condition it is somewhat remarkable that no clinical evidences of specific vitamin deficiency were discovered. The delicacy of the skin was interesting and while it was dry and in places scaly, the usual, swollen, infiltrated appearance of myxedema was entirely lacking. It resembled the skin of a very old individual or the skin seen in advanced cases of Cushing's syndrome. The extensive purpura was thought to be similar to that observed in senile atrophy and in other atrophic and wasting conditions of the skin, an inference which was strengthened by our failure to show any defects in the clotting mechanism.

From a pathological standpoint the case is perhaps chiefly remarkable because of the numbers of tissues minutely examined for manifestations of hypothyroidism. In evaluating these changes we have assumed from the appearance of the thyroid gland that its function was totally lost, a condition which, on the basis of anatomical evidence, may be regarded as quite rare. It can be further assumed that because the condition had lasted for a long time, the anatomical changes should be regarded as maximum.

The microscopic changes in the skin afforded no surprise. The parakeratosis, the atrophy of the epithelium and its adnexae, and the perivascular, lymphocytic infiltration are typical of the skin in myxedema. Edema of the collagen as observed in this case has also been described (5). The classical, so-called mucinous infiltration of the dermis is not always found.

The presence of gross changes in the heart muscle in myxedema was first described by Ord (6) in 1880. Accompanying mucinous degeneration has been described in some cases (2, 7–10), and has not been evident in others (11–13). In the instances in which no such changes were seen it is possible either that hypothyroidism had not been present long enough to cause them or that they were overlooked. Experimentally it is evident from the work of Webster and Cooke (2) that such changes can be produced in rabbits if the animals are subjected to deprivation of thyroid secretion for a reasonable length of time. The essential change in this case, i.e., degeneration of the muscle cells, is similar to that described by Webster and Cooke in animals and by others (10, 14), in humans. Some previously observed changes in the myocardium such as the increase in the number of nuclei and grouping of the nuclei are not pronounced in these sections. There would appear to be no doubt that the lesions described by Cooke and Webster (2), Tatum (7), and Behr and Mulder (10) are identical with those seen in this patient.

In varying degree the change is the same in the heart, striated muscle, and in the smooth muscle of the gall bladder, uterus, and urinary bladder. Larger lesions in the cardiac and striated muscles may have been attributable to the greater size of the affected cells. The intense edema of the muscular layers as apparent in the sigmoid of our case has been described by Tatum (7) and others. Both edema and basophilic degeneration were present throughout the sigmoid but were more evident in the dilated segment. The change in the smooth muscle of the urinary bladder resembled that observed in those portions of the intestine which were of relatively normal caliber. In the uterus there was slight degeneration of the smooth muscle, but the most marked change was in the walls of the uterine arteries. In some areas this was identical with that observed in the wall of the aorta, but in others was so advanced as to constitute total destruction of the media of the arterial wall.

Morphologically all lesions in muscle were identical and varied only in degree. The cystic degeneration in the aorta described by Erdheim (4) as idiopathic cystic medial necrosis of the aorta and that seen in the cases presented by Kountz and Hempelmann (3) cannot be differentiated from the change in this aorta. Identity is further established by similarity of appearance in the lesions in various organs under different staining techniques. The substance in the aortic and other muscular le-

sions when stained with hematoxylin and eosin is basophilic and homogeneous to granular. With Heidenhain's stain it is light blue and when stained with cresyl violet is light purple.

The nature of the substance in the vacuoles, although thought to be serous fluid by some observers, is not that of a simple transudate. In formalin it is coagulated in such a manner as to give it a homogeneous appearance. With mercuric chloride the precipitate is in the form of granules and droplets. Precipitation and staining reactions are similar to those of fibroblastic mucin and are the same as those obtained in this laboratory by Kountz and Hempelmann in the chromatropic degeneration of ruptured aortas. The reactions suggest that the material is a form of mucoid. The variation in structure of the vacuoles is explained by Mallory who describes mucin as being precipitated as strands, smooth homogeneous masses, or small droplets by different fixation methods.

Lesions of muscles in myxedema have been emphasized since the earliest descriptions. It has also been noted that basophilic infiltration and degenerations of muscle fibers might be evident in smooth muscle and skeletal muscle as well as in the heart. There has also been speculation concerning the role of these pathological changes in the dilatation of the heart in myxedema. Their possible importance in the function or adequacy of other muscles has however been little emphasized. That they may have been responsible for the gross sigmoidal dilatation of the sigmoid colon in this case is apparent. Moreover, changes as extensive as those observed in the uterine arteries of our patient might obviously lead to weakness of vessel walls. Their possible practical significance has been indicated by the observations of Kountz and Hempelmann on spontaneous rupture of the aorta. The changes in the aortic walls of their cases of induced hypothyroidism coincided exactly in appearance and in staining reactions with those here described. The fact that they were also indistinguishable from the chromatotropic degeneration described by Erdheim suggests that at times hypothyroidism may contribute to medial necrosis of the arterial wall and consequent spontaneous aortic rupture on dissecting aortic aneurysm.

The degree to which undernutrition may have contributed to certain aspects of this case cannot be accurately evaluated. That it was not responsible for the muscle lesions is indicated by the similarity of the changes to those both in previously autopsied cases of myxedema and in experimental hypothyroidism, in animals.

SUMMARY

Report is made of a long-standing fatal case of myxedema. Clinically it was characterized by atrophy of the skin, purpura, hypocholesterinemia, hypoproteinemia, ascites and gross segmental dilatation of the sigmoid colon.

Pathologically it was characterized by lesions of muscle cells consisting of degeneration of the central portion of the sarcoplasm with the production of vacuoles containing a basophilic granular or homogeneous material.

Identical lesions were demonstrable in cardiac and skeletal muscles and in the muscular coats of the esophagus, sigmoid colon, gall bladder, urinary bladder and uterus. It appeared that the segmental dilatation of the sigmoid colon was dependent upon edema and degeneration of the muscle of the intestinal wall.

Staining and precipitation reactions indicate that the substance in the vacuoles may be related to fibroblastic mucoid.

The lesions in the muscles in this case are morphologically similar to those described by Erdheim as idiopathic cystic medial necrosis and to those seen by Kountz and Hempelmann in spontaneous rupture of the aorta in induced hypothyroidism.

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Problems in the Treatment of Cardiac Failure in Myxedema

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THE SPECIFIC origin of myxedema in thyroid deficiency implies a therapy so simple and so adequate as to warrant little amplification. However, it has long been recognized that all types of hypothyroid patients tolerate thyroid hormone less well than individuals with normal basal metabolic rates. Moreover, Means and his associates (1) have demonstrated rather clearly that the actual initial and maintenance dosages to be used vary considerably from subject to subject. Some of their patients needed 3 grains of desiccated thyroid substance daily; others were relieved of the majority of their symptoms with as little as ½ grain daily, although basal metabolic rates were never normal with this amount of material. In the majority of patients, this problem of tolerance is dependent upon cardiovascular disturbances. These may be due solely to the myxedematous state, or may represent pre-existing lesions which are aggravated by the metabolic changes present in myxedema. The heart of the subject with long-standing myxedema rarely escapes; the older the individual, the more diffuse and irreparable the damage. Some patients are in cardiac failure when first seen; in many others, failure is precipitated through the added load which treatment places upon the already under-privileged heart. The problems of the clinician are still further multiplied through the fact that cardiac failure tends to destroy or distort the sign posts by which he is accustomed to gauge the progress of the condition. We refer to the directly opposite effects of congestive failure and myxedema upon the pulse and the basal metabolic rate, and to the unreliability of variations in weight and circulation time when the two co-exist. It would appear to be a simple matter to overlook the myxedema and treat the cardiac failure, but such a course would ignore the fact that at least a part of the cardiac difficulty arises out of the thyroid deficiency (2–6). Therefore, the solution to the physician's problem lies in the application of thyroid hormone in dosages sufficiently great to improve the nutritional status of the heart and yet so small as to raise the cardiac load only very gradually. Since not only the success of the treatment but also the very life of the patient depends upon the careful appraisal of the two factors just mentioned, an attempt has been made to formulate reliable criteria for the early detection of the *trend* of therapy. It is obviously impossible to give these patients full doses of hormonal therapy without disaster. It is, therefore, necessary to carry treatment forward over a period not of days but of months, during which the hypothyroid state is slowly overcome. Even with the greatest precautions, supportive cardiac therapy may be necessary.

Read at the Twenty-Seventh Annual Meeting of the Association for the Study of Internal Secretions, at Chicago, June 12, 1944.

MATERIAL AND METHODS

Twenty-four patients with myxedema, 20 female and 4 male, have served as the basis of the study. Twenty of these were admitted because of cardiac failure. Among the 24 patients, there have been nine deaths, followed in five by autopsy. One of the patients, having congenital myxedema with patent ductus arteriosus and

other anomalies, died at the age of nine months. The remaining eight deaths resulted directly from the cardiac complications of the myxedematous state.

The average age of the 24 patients was 52.1 years, the youngest and only congenital or childhood case being admitted at birth, and the oldest, at the age of 71 years. The average age of onset of the disease in 18 patients was 39.2 years. In 18 patients, the time which elapsed from the appearance of symptoms until the true nature of the condition was recognized ranged from three months to 13 years, with an average of 4.2 years.

Myxedema was the only precipitating factor that could be found in the cardiac failure of four patients. Of the remaining 16 admitted with right or left failure or both, generalized arteriosclerosis was noted in 12, with demonstrable coronary sclerosis in nine, three of whom had developed coronary thrombosis shortly before entrance to the hospital. Hypertension was present in seven cases, and syphilis, diabetes mellitus, and thrombosis of the pulmonary artery each in one instance. The heart was demonstrably enlarged in all but one patient. Nine patients showed left-sided failure only, which varied in degree from dyspnea on exertion in four to bouts of pulmonary edema in two. Right-sided and left-sided failure were concomitantly present in 10 instances, and congestive failure alone in one. An initial low-voltage in all complexes of the electrocardiogram was seen in 13 patients. The complete histories and further details of the cardiac status of these patients will be reported elsewhere (7).

Eight of the 20 patients admitted for cardiac failure died. Five of the eight received no thyroid medication, although two survived a period of 21 and 41 days, respectively. In all, 13 patients were treated with desiccated thyroid in conjunction with cardiac therapy as indicated. All patients remained in the hospital throughout the period of observation. The progress of treatment was followed by serial examination of five or more of the following: weight, pulse rate, basal metabolic rate, blood cholesterol, circulation time, capillary permeability, electrocardiographic tracings, and roentgenography of the heart and lungs. Estimations of glucose, free cholesterol, total proteins and protein partition, and phosphatase were discarded in the analysis of data for the following reasons. Blood glucose and phosphatase were always normal. Free cholesterol moved in consonance with the total cholesterol, remaining a normal fraction of the latter, except in severe forms of longstanding cardiac failure with "cardiac cirrhosis." Blood proteins were more frequently high than not in the untreated patients with myxedema (7, 8), but variations under treatment bore no significant relationship to the patient's clinical condition.

Capillary permeability and circulation time were estimated by the fluorescein methods of Lange (9, 10). Blood cholesterol was determined by Drekter's modification (11). Antigen for the cephalin flocculation test was prepared according to the method of Thudichum (12) using an especially prepared cholesterol.[1] All other recorded determinations have been made with standard procedures that are in common clinical laboratory usage. Slight deviations in the securing of blood specimens and in the amounts of serum used for various tests have been described elsewhere (13).

RESULTS AND DISCUSSION

A. *Therapy.* Desiccated thyroid was given to 13 patients. The initial dose is shown in the following table.

TABLE I. INITIAL DOSE OF THYROID ADMINISTERED TO 13 PATIENTS WITH MYXEDEMA

Number of Patients	Thyroid (grains per day)
3	0.05
1	0.10
4	0.25
3	0.50
1	1.0
1	3.0

There were no untoward reactions in any patient from 0.05 grain daily, and objective improvement could be observed in patients so treated. The one patient started on 0.1 grain daily required a reduction to 0.05 grain in order to relieve a severe angina pectoris. It was not possible to relieve the myxedema completely in any patient who took 0.05 to 0.1 grain daily. Of the patients initially placed

[1] Manufactured by the American Cholesterol Products Co., Milltown, N. J.

upon 0.25 grain per day, two did well; and in two the dose was decreased to 0.1 grain—in one because of an anginal syndrome, and in the other because of right-heart decompensation. One of the three initially taking 0.5 grain per day developed anginal symptoms necessitating a reduction to 0.25 grain daily; the other two had little or no difficulty. The case which was at first given 1 grain daily was mild in character and responded satisfactorily. The patient receiving 3 grains daily as a starting dose succumbed to both right and left heart failure on the sixth day of treatment. The large dose of thyroid hormone was believed to be a major precipitating factor in her death.

In all there were three deaths among the patients who received hormonal therapy. The second occurred in a 60-year-old woman with advanced arteriosclerosis and arteriosclerotic heart disease (*K.B., Case no. 17*) who entered the hospital with severe right and left heart cardiac failure and died on the twenty-sixth day after admission. Thyroid was withheld until the eighteenth day with the hope of first improving the cardiac status. As this failed, thyroid was started in 0.05 grain doses daily in conjunction with other therapy. It seems unlikely that it played any part in the final outcome. The third death was that of a 63-year-old woman (*G.F., Case no. 16*) who died on the 135th day of hospitalization. She had been admitted following coronary thrombosis with both right and left failure. After recovery from the acute attack, thyroid hormone in doses of 0.10 grain daily was given. Anginal pain occurred 13 days later, so severe in character that the drug was stopped. After all pain had ceased (14 days later), the hormone was again begun, however, in a dose of 0.05 grain daily for 14 days without untoward symptoms. One-tenth grain daily was then given for 20 days without symptoms. The patient's myxedema had begun to improve as shown by a decrease in capillary permeability from plus 165 per cent to plus 70 per cent; an increase in basal metabolic rate from minus 42 per cent to minus 20 per cent; and a change in blood cholesterol from 580 to 360 mg. per 100 cc. When the report of the minus 20 per cent basal metabolic rate was received, the dose was inadvertently raised from 0.10 grain to 1.0 grain daily. On the fourth day thereafter, the patient had severe anginal pain, and on the sixth day died from a fresh coronary occlusion. While a causal relationship cannot be unequivocally established, it seems logical to suppose that the increased heart load was at least one precipitating factor in the final episode of life. Prior to the change in medication, she had been well and had been free from precordial pain for nearly two months, as compared with the early part of her hospitalization, during which it had been continuously present.

Smyth (14) reviewed the literature in regard to angina pectoris and myocardial infarction as complications of myxedema. While he stressed the possibility of coincidence, several of the cases he cited had aggravation of cardiac symptoms as a result of the administration of thyroid substance; on the other hand, others showed improvement in them by the use of *gradually* increasing doses of the hormone. The careful correlation of data in Beaumont and Robertson's case (5) leaves little doubt as to the precipitating role of larger doses of thyroid in the anginal pain, and the gradual removal of pain by the judicious use of gradually increasing amounts. Zondek emphasizes the same point (6). Bartels and Bell (2) have shown the high incidence of coronary sclerosis in myxedema and the dangers inherent therein; the dosage of thyroid had to be decreased in several of their patients to relieve the angina and, later, could be brought back to the initial levels. While it is common knowledge that the "high cholesterol arteriosclerosis of rabbits" may disappear on reversion to normal diet, it seems dubious that a material regression in sclerotic changes of the coronary artery should be postulated as a result of thyroid treatment of the patient having myxedema. Perhaps more light is thrown upon the mechanism by which the nutrition of the myxedematous heart is improved by the work of Stewart and his associates (15). They found that the cardiac output per minute and per beat diminished in myxedema, with correspondingly slow velocity of the blood. Despite the lowered basal metabolic rate, they demonstrated an increased arteriovenous oxygen difference, presumptively as a result of the markedly diminished cardiac efficiency. The heart

muscle itself must obviously share in the poor nutritional state as repeatedly demonstrated by its change in size (16, 17, 6, 3, 14, 18, 19) and the findings at post-mortem (3, 4). For these reasons the load of the heart must be increased very slowly to avoid cardiac complications during treatment. Otherwise, coronary insufficiency with clinical manifestations which range from mild angina to myocardial infarction may occur.

B. *Appraisal of weight, pulse rate, and certain laboratory procedures in following the therapy of patients with myxedema.* The obvious aim of the clinician throughout his treatment of a myxedematous patient with cardiac failure is to relieve the myxedema without critically influencing the heart. Aids to the charting of such a course have not been very satisfactory. We shall briefly analyze the results of our observations in the seven patients (Nos. 2, 5, 6, 8, 9, 22, and 24) who were followed to a satisfactory solution of their myxedematous process.

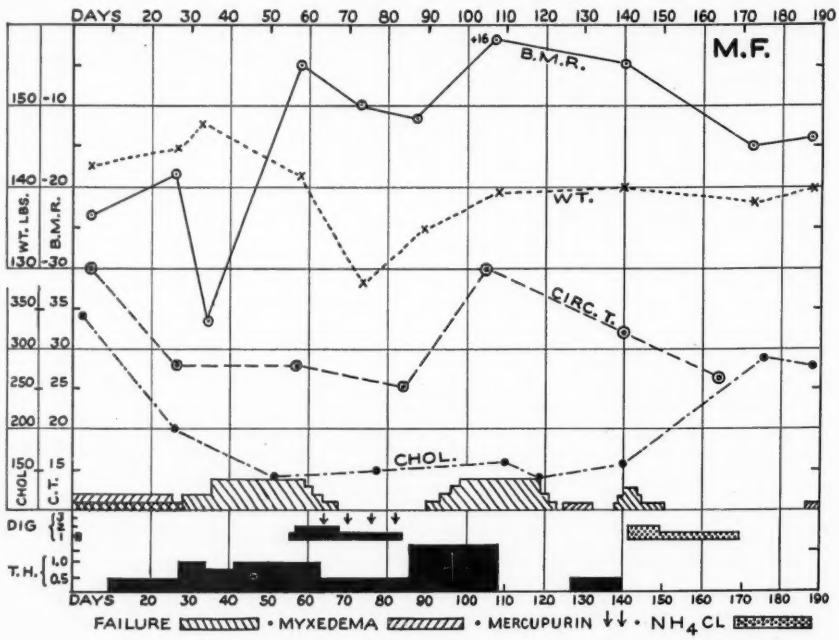

FIG. 1A

Seven of the 13 patients were followed until fully stabilized on thyroid hormone. The following table shows the dosages necessary for complete relief of all the symptoms of the myxedema as gauged by subjective symptoms, objective signs, and changes to normal in the results of the laboratory procedures above mentioned.

TABLE II. STABILIZATION DOSE OF THYROID ADMINISTERED TO 7 PATIENTS WITH MYXEDEMA

Number of Patients	Thyroid Hormone (grains daily)
4	1.0
1	1.5
1	2.0
1	3.0

1. *Weight, pulse rate, circulation time, and basal metabolic rate.* Weight was stationary in four of the seven patients, with minor fluctuations related to the extent of edema present; it dropped appreciably in two due to relief of right-heart failure and rose in one, presumptively as the result of improvement in the general condition.

The pulse rate was equally deceptive as a guide to therapy. In a patient with an uncomplicated case of myxedema, a steady rise from an abnormally low to a normal rate would be expected. In two patients this occurred; cardiac symptoms were minimal in both. Its be-

havior was most irregular in the others and of no value as a guide to treatment.

The circulation time was initially prolonged in five of the seven patients in whom it was measured. It fell well within the upper range or normal in three of these after satisfactory treatment, but remained abnormally high in the other two, although somewhat decreased from the original levels. It was subject to considerable fluctuation during the course of treatment, as may be seen from the charts of *Case No. 24, M. F.* (fig. 1A and 1B). At no time could it be said to indicate only the status of the thyroid.

The average basal metabolic rate of these seven patients at the beginning of treatment was minus 29, and after satisfactory treatment, was minus 10. However, this definite over-all change for the better does not in any way reflect the intermediate variations that occurred during the stages when myocardial failure and myxedema co-existed. Rapid elevations and depressions occurred in the five patients who at one time or another exhibited the more severe cardiac symptoms. Such changes are well illustrated by the charts of *Case No. 24* (fig. 1A and 1B). For instance, when she was in severe cardiac failure and receiving 1.5 grains of thyroid daily, the basal metabolic rate was plus 16. Thyroid medication was stopped; as soon as the cardiac condition improved, the true basal metabolic rate of minus 25 per cent was elicited. A similar change is noted during her first days in the hospital and again between the 350th and 375th days of her stay. *In the face of cardiac complications, the basal metabolic rate should not be relied upon to afford a true picture of the status of therapy.*

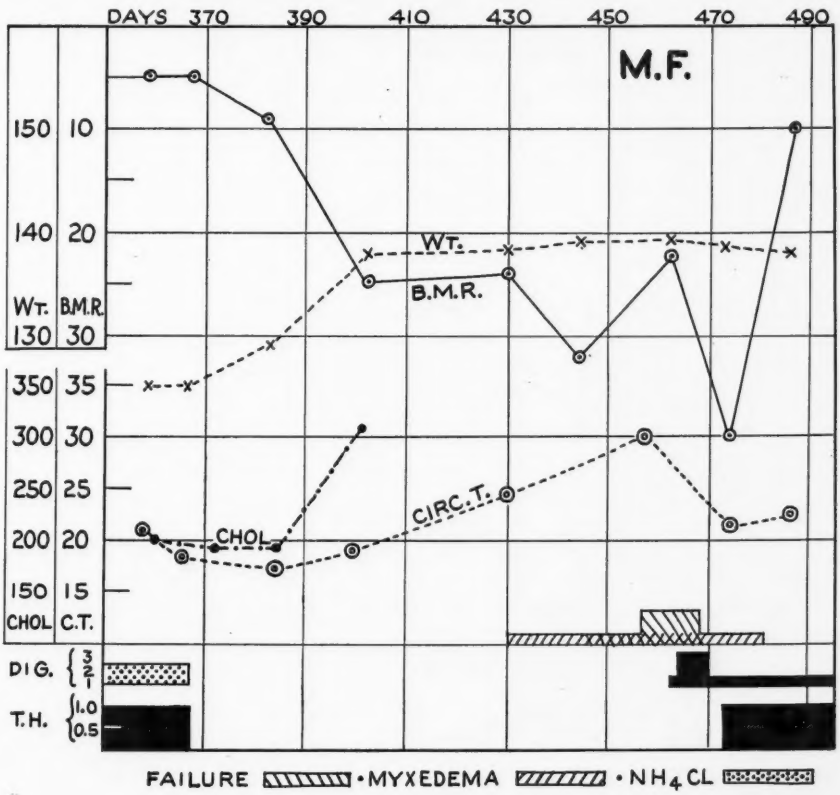

FIG. 1B

2. *Blood cholesterol.* The blood cholesterol was above 200 mg. per 100 cc. in 14 of 18 pa-

tients. This and other initial laboratory data in the 24 patients studied are recorded in detail elsewhere (7, 8). On admission the blood cholesterol for the group was 364 mg. per 100 cc. on the average. In the seven patients followed to a satisfactory stage of therapy, the initial value averaged 366 mg. per 100 cc. with cholesterol to the administration of thyroid hormone. On doses of as little as 0.05 grain daily, her blood cholesterol decreased from an initial level of 535 mg. per 100 cc. to 340 mg. per 100 cc., attained a value of 240 mg. per 100 cc. after ten days of treatment with 0.25 grain daily, followed by six days on a dose of 0.5

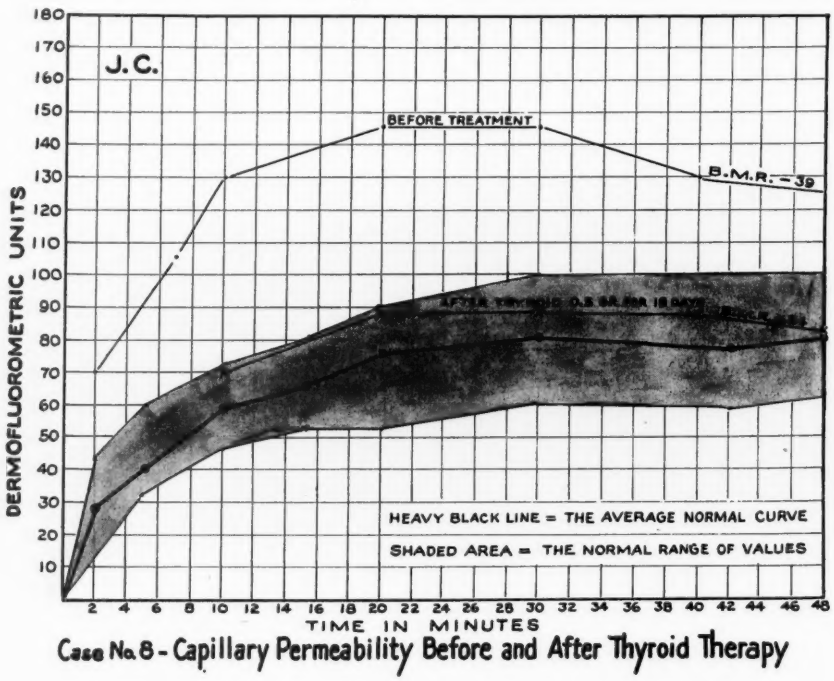
J.C.
BEFORE TREATMENT
B.M.R. - 39
DERMOFLUOROMETRIC UNITS
HEAVY BLACK LINE = THE AVERAGE NORMAL CURVE
SHADED AREA = THE NORMAL RANGE OF VALUES
TIME IN MINUTES
Case No. 8 - Capillary Permeability Before and After Thyroid Therapy

FIG. 2

the lowest figure 190, and the highest 558 mg. per 100 cc. At the conclusion of the study, the average was 158 mg. per 100 cc., with a low of 130, and a high of 200 mg. per 100 cc. The fluctuations of total blood cholesterol were not influenced by either right or left heart failure. While they sometimes changed slowly, their alterations usually reflected the thyroid status. For each individual it is important to know the pretreatment levels of cholesterol in order to determine the significance of any change in therapy. In a patient with a cardiac disturbance whose blood cholesterol is falling, even though slowly, under a given dose of thyroid hormone, we favor no further increase until the blood cholesterol has "levelled off." *R.W.* (*Case No. 9*) demonstrates the response of grain. It was finally maintained at or below 200 mg. per cent on 3 grains daily when all signs and symptoms of myxedema had disappeared. *The variations in the concentration of cholesterol are as reliable as changes in capillary permeability but, as a rule, occur less rapidly.* The basal metabolic rate increases at the same time, provided no cardiac complication exists.

3. *Capillary permeability.* In a previous series of experiments, capillary permeability as quantitatively estimated by the method of Lange was found to be within normal limits in patients with either right-sided or left-sided cardiac failure or both (20). In all of eight case of myxedema in which it was estimated, it was exceptionally high, reaching 156 per cent above the average for normal individuals (8). Serial

examinations were made in three of the seven cases who were followed until myxedematous symptoms disappeared; in each of these the capillary permeability was normal at the time of discharge. These changes are illustrated by figs. 2 and 3, the findings in *J. C.* (*Case No. 8*) *R. S.*) the initially high curve became normal while the pulse rate rose from 56 to 70, the blood cholesterol dropped from 600 to 350 mg. per 100 cc., the circulation time decreased from 22 to 20 seconds, and the basal metabolic rate declined from minus 33 to minus 38 per cent.

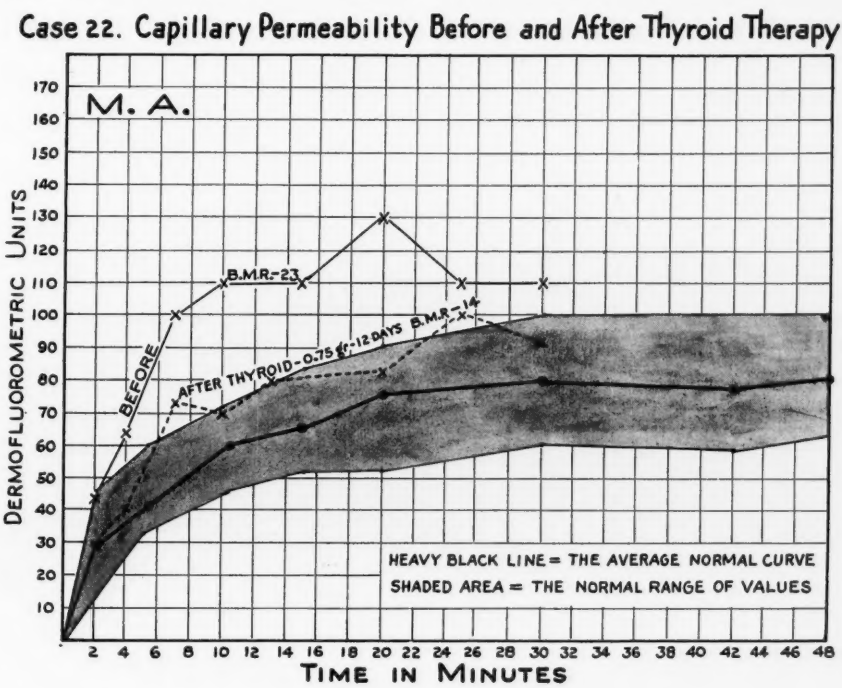
Case 22. Capillary Permeability Before and After Thyroid Therapy
M. A.
DERMOFLUOROMETRIC UNITS
TIME IN MINUTES
B.M.R.-23
BEFORE
AFTER THYROID-0.75 gr.-12 DAYS B.M.R.-14
HEAVY BLACK LINE = THE AVERAGE NORMAL CURVE
SHADED AREA = THE NORMAL RANGE OF VALUES

FIG. 3

and *M. A.* (*Case No. 22*), respectively. In both instances, it may be noted that the curves after treatment fell within the range of normal before the basal metabolic rate gave evidence of complete restoration of thyroid-hormone activity. This was also true of the third case, the "before" and "after" curves of which have been reproduced elsewhere (8). In fact, it is our belief from limited observation that a *decrease in capillary permeability is the earliest objective change toward normal in the myxedematous state.* This concept is further supported by "follow-up" curves determined on three patients who improved in the hospital but were not brought to a state of hormonal balance. In one of these (*Case No. 17, K. B.*), the capillary permeability decreased, but no comparative data were available. In a second (*Case No. 11,* Clinically, the patient was improved, and the change in metabolic rate must be ascribed to improvement in her cardiac status. In the third patient (*Case No. 16, G. F.*) the permeability decreased from a very high level to a lower but still not normal curve, while the basal metabolic rate rose from minus 42 to minus 20 per cent, and the blood cholesterol decreased from 580 to 360 mg. per 100 cc. This patient was improved under thyroid therapy but was never relieved of her myxedematous state by the doses of hormone that could be tolerated.

The rapid flooding of the tissues with fluorescein in these patients suggests some change which favors the passage of material from the capillaries to the tissues. That this is not a simple dilatation of the capillary loops seems to have been shown by Zondek, Michael, and

Kaatz (21). On the contrary, they found a decreased number of much narrowed, little tortuous, and short ungual loops. They were at a loss to explain the similarity between these findings and the nearly identical ones seen in hyperthyroidism. These changes disappeared when the patient was fully treated with thyroid substance but no straight-line correlation

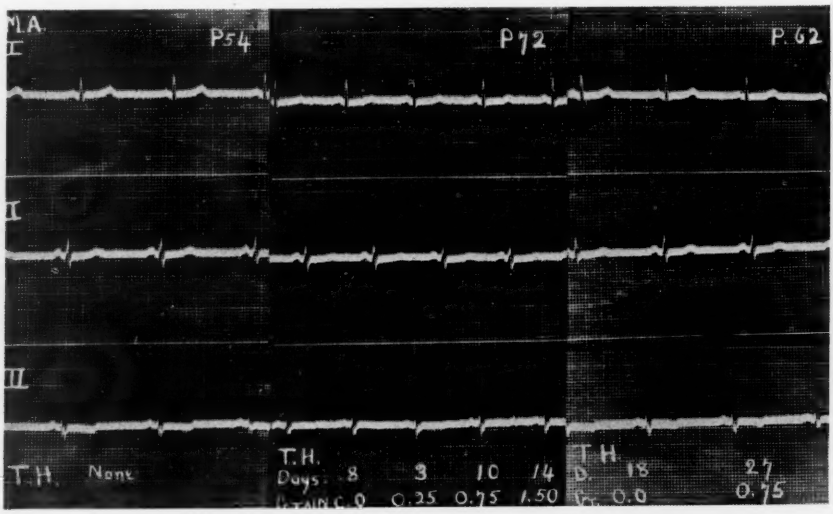

FIG. 4. Electrocardiographic tracings of *M. A., Case No. 22.* A. On admission to the hospital a bradycardia was present; otherwise the tracing was normal. B. Tracing on the thirty-fifth day of hospitalization, following the use of 0.25 grain daily of thyroid for three days; 0.75 grain daily for ten days; and 1.50 grains daily for 14 days. Note the lowering of the T-waves in leads I and II and their absence from lead III, which together with exacerbation of her angina suggested an increasing cardiac strain. This tracing was of value in showing the necessity for a reduction in the dosage of thyroid. C. Tracing made on the eightieth day of hospitalization. Note the reversion of the electrocardiogram to normal (except for bradycardia) after cessation of therapy for 18 days followed by 0.75 grain of desiccated thyroid daily for 27 days. Symbols and abbreviations on the tracings are explained in the legend for fig. 5.

existed between the degree of these changes and the basal metabolic rate or the clinical condition.

4. *Electrocardiographic tracings.* Serial electrocardiograms were made in seven of the 13 patients receiving thyroid medication. In five of these, all of the complexes initially showed a low voltage. It seems unnecessary to detail other electrocardiographic findings here. These five were among the seven patients whose myxedematous state was relieved under therapy. In each instance the low voltages eventually reverted to normal. In three of these patients (*Cases No. 8, 9,* and *22*) in whom electrocardiographic tracings and determinations of capillary permeability were made simultaneously, it was shown that *the low voltage of the electrocardiogram reverts to normal at approximately the same time that capillary permeability is no longer disturbed.* The electrocardiogram has served another useful purpose in warning of increasing cardiac damage when the amount of thyroid administered is not well tolerated. This may be noted in patient *M. A.* (*Case No. 22,* fig. 4). The patient had been subject to vague pains in the left chest throughout her hospitalization. When she complained of exacerbation of these on or about the 35th day, the electrocardiogram served to confirm the presence of increasing cardiac damage as a result of administering 1.5 grains of thyroid daily. Note the low T-waves in leads I and II and the absence of a T-wave in lead III. She had had 1.5 grains of desiccated thyroid substance daily for 14 days previously. After stopping the hormone for 18 days, she was able to use 0.75 grain daily without untoward symptoms. Later she was fully stabilized without distress on 1.5 grains daily, the dose she had not tolerated earlier in the treatment. Her experience again emphasizes the importance of beginning the treatment with small doses of hormone. The

actual dose which will be tolerated seems to bear a direct relationship to the degree of myocardial damage and an inverse relationship to the age and duration of the disease.

The interplay of cardiac failure and myxedema is well illustrated by selected electrocardiograms (fig. 5) taken on *M. F.* (*Case No. 24*) whose clinical course is depicted in figures 1A and 1B. On admission to the hospital with mild left-sided failure and severe myxedema, the predominant findings were a pulse rate of 52 and a low voltage of all complexes in all limb leads (fig. 5A). The prolongation of the P-R interval appeared to be due to an old lesion and a constant finding in all her tracings, so it will not be mentioned again. Figure 5B shows the changes resulting from severe cardiac failure on the 49th day after admission. In the interim the patient had received some thyroid therapy as noted. The rate was approximately 120, the low voltage had been increased, and severe myocardial failure was present. The last-mentioned was controlled by digitalis therapy, and thyroid treatment was continued so that on the 72nd day of hospitalization, the electrocardiogram could be looked upon as normal with the exception of a digitalis effect reflected in the configuration of the T-waves (fig. 5C). Figure 5D represents the patient's electrocardiographic status on the 444th day of hospitalization, 77 days after hormonal and cardiac therapy were stopped. Clinical evidences of myxedema were present, including a rising cholesterol and a falling basal metabolic rate (fig. 1B). A lowering of voltage was again observed in all complexes of all leads. The final tracing (fig. 5E) was taken on the 522nd day of hospitalization, with the patient completely controlled on 1.5 grains of digitalis and 1 grain of desiccated thyroid daily. The electrocardiogram was normal. While other findings were more suitable than the electrocardiogram for directing therapy in this as well as in the other patients, the alterations to be seen in the latter were confirmatory in nature and on more than one occasion gave forewarning of impending cardiac insufficiency.

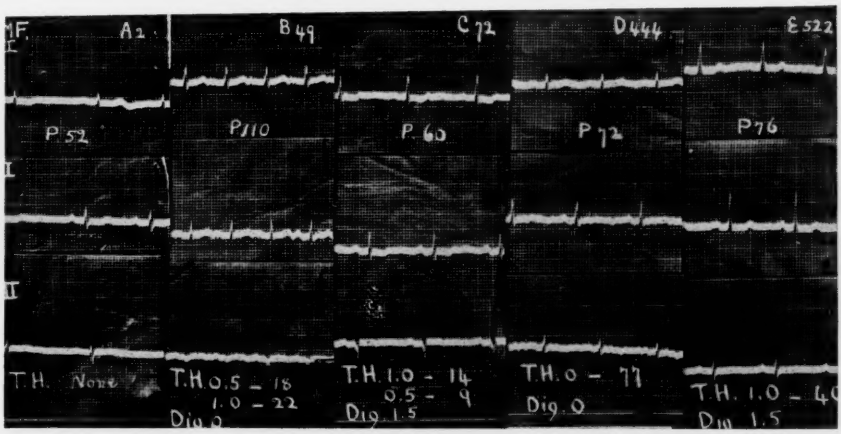

FIG. 5. Electrocardiographic tracings of *M. F., Case No. 25.* The tracings are serially lettered from A to E; the day of hospitalization is indicated by the figure to the right of each letter. The pulse rate per minute is indicated by P; the daily dose of thyroid hormone in grains, by T.H.; and that of digitalis in grains, by the abbreviation Dig. In each instance, the figure to the right of the dash represents the number of days through which the indicated therapy was used prior to taking the tracing. A. A tracing taken before treatment was begun. Note the bradycardia and low voltage in all complexes of all leads. B. A tracing taken while in cardiac failure following the use of thyroid hormone, 0.5 grain for 13 days, and 1.0 grain for 22 days. Note the absence of features pointing to myxedema. C. A normal electrocardiogram (except for T-waves) following combined thyroid and digitalis therapy as noted on the tracing; the T-wave changes were believed to be due to digitalis. D. After 77 days without thyroid or digitalis therapy; myxedema was present; compare with tracing A. E. Completely normal electrocardiogram after 40 days of thyroid, 1 grain daily, and digitalis, 1.5 grains daily. Clinically the patient's cardiac condition was fully compensated, and her thyroid status satisfactory, with a basal metabolic rate of minus 7 per cent.

5. *Roentgenography of the heart and lungs.* Serial roentgenograms of the heart and lungs were taken in but one of the four patients whose cardiac condition was believed to be due solely to the myxedematous state (*Case No. 9,*

R. W.). In this patient, a slightly enlarged heart with a cardio-thoracic ratio of 0.51 was found, which decreased to within normal limits (a cardio-thoracic ratio of 0.48) under adequate hormonal therapy. It is probable that the changes seen in three other patients were due in part to an improved thyroid status, but this is difficult to prove, as hypertension and/or cardiac failure were simultaneously present. *The complicating cardiac conditions would seem to preclude the extended use of roentgenography as a guide to therapy.*

The cause of the large heart in uncomplicated myxedema and its complete return to normal size under treatment is still a subject for speculation. The original concept that the enlargement is usually the result of some degree of pericardial effusion seems long since to have been exploded (16, 22). Cellular and intercellular changes in the cardiac musculature itself seem to account for the alterations usually noted (3). LaDue called attention to the similarity between these histological changes and those seen in vitamin-B deficiency (beriberi) (3).

The decrease in the size of the heart with improvement in its function under thyroid therapy has been mentioned by a number of workers (4, 5, 15, 16, 19, 23). This improvement appears to be a specific response, since LaDue clearly demonstrated that vitamin administration had no influence upon it (3). Stewart, Deitrick, and Crane believe the ability of thyroid hormone to decrease the circulation time and the arterio-venous oxygen difference improves the nutrition of the heart muscle, and thus, its efficiency (15). Zondek and his associates (21) present a rather mechanical explanation of the cardiac disturbances in hypothyroidism which demands their postulating a higher tissue than vascular pressure. They suggest that the cellular and interstitial edema tends to constrict the capillaries of the heart in a fashion similar to that seen in the ungual loops. In their opinion, this also explains the presence of the anginal syndrome so frequently seen in hypothyroid states and affords a reason for the frequency of coronary occlusions. The appearance of heart symptoms in the untreated hypothyroid subject from even the smallest doses of hormone and the later ability to take without any unpleasant symptoms several times the initially tolerated dose does justify the conclusion that an atheromatous process is probably not the basis of the observed angina (2–6, 14, 17, 18). In uncomplicated cases of the present series, there was a close parallel under treatment between the increased amplitude of all the electrocardiographic complexes, a reduction in the size of the heart, and a return of the capillary permeability to normal. This would lead us to believe that the *alterations in the cardiac configuration as a result purely of myxedema are intimately connected with capillary, interstitial, and tissue cell changes, the nature of which is rather readily reversible.*

CASE REPORTS

An analysis of all case histories will appear elsewhere (8). The records of the two patients whose findings have been used extensively for illustrative purposes are summarized below. The case numbers refer to the chronological position in the series as a whole.

Case No. 22, M. A., a 55-year-old, white woman was admitted to the hospital complaining of ease of fatigue, drowsiness during the day, insomnia, cough, dyspnea on exertion, and edema of the ankles toward evening. The first three of these manifestations had been present more or less continuously since her menopause ten years before. Even the effort of combing her hair "completely exhausted" her. Not only was her sleep much broken at night, but she was unrefreshed on awakening in the morning. She attributed her cough to a chronic bronchitis which had become progressively worse during the preceding 15 years. Dyspnea on exertion and the ankle edema had been present intermittently for three months. She had had pneumonia "several times" as a child and had had chronic bronchitis for many years. Her menstrual periods began at the age of 11 years, had recurred every 28 to 30 days until the age of 45 years, and had lasted from six to nine days with moderate flow. She had had a tonsillectomy at the age of 6, a partial salpingo-oöphorectomy at the age of 16 years, and a perineorrhaphy at the age of 49 years. Her family history was irrelevant. Physical examination revealed a rather expressionless, pasty-faced, sluggish individual, answering questions accurately in a dry, hoarse voice after some hesitation. Her skin and hair were dry and coarse. The thyroid was not enlarged. The lungs were moderately emphysematous, but otherwise revealed no acute or chronic pathology. The heart outline was difficult to delineate because of the emphysema. However, the apex beat was 3 cm. beyond the midclavicular line. The heart sounds were distant, especially over the aortic area. The apical rate was 54 per minute, and the blood pres-

sure, 130/85 mm. Hg. Abdominal examination revealed normal conditions. The deep tendon reflexes were sluggish.

Laboratory data obtained on or shortly after admission included negative blood Wassermann and Kahn reactions; a negative direct van den Bergh response; an absence of cephalin-cholesterol flocculation; an icteric index of 6 units; and a basal metabolic rate of minus 23 per cent. The urinalysis revealed no abnormal findings save the presence of a few hyaline casts. Her hemoglobin was 82 per cent. She had 4,580,000 erythrocytes and 5,035 leucocytes per cu. mm. of blood. The distribution of white cells was as follows: polymorphonuclear leucocytes, 49%; lymphocytes, 46%; eosinophiles, 4%; and basophiles, 1%. The total serum protein was 9.5% with an albumin fraction of 5.9 gm. per 100 cc., and an albumin-globulin ratio of 1.6. Other blood chemical constituents in milligrams per 100 cc. were as follows: urea nitrogen, 15.0; creatinine, 1.3; glucose, 110; ascorbic acid, 0.5; phosphorus, 4.3; alkaline phosphatase, 5.0; total cholesterol, 310; cholesterol esters, 190; free cholesterol, 120 (39 per cent). Her circulation time (fluorescein—arm to lip) was 18 seconds. Her capillary permeability (9, 10) was increased (fig. 3). Her electrocardiographic tracing was normal (fig. 4). Roentgenograms revealed a large heart. Retrograde pyelograms showed an ectopic left kidney lying close to the midline just above the inlet of the true pelvis.

Diagnosis: Myxedema with mild left ventricular failure; obesity of endocrine origin; ectopic left kidney.

Course in the hospital: This patient was under observation in the hospital for 84 days. Despite her history, no edema of the extremities was noted at any time during her hospital stay. With bed rest alone, her manifestations of left-heart strain disappeared promptly, so that she was placed upon desiccated thyroid substance, 0.25 grain daily, on the eighth day of hospitalization. This was increased to 0.75 grain daily on the 12th day, and again increased to 1.5 grains daily on the 26th day after entering the hospital. On this regimen, her myxedematous state improved by the 40th day of hospitalization; her circulation time dropped from 18 to 14 seconds, and her pulse and basal metabolic rate rose from 54 to 72 and from minus 23 to minus 12 per cent respectively. However, anginal symptoms and dyspnea on the slightest exertion had made their appearance. In view of the electrocardiographic changes (fig. 4), desiccated thyroid substance was discontinued for 18 days, during which the myxedematous state returned but with the disappearance of all cardiac symptoms and electrocardiographic alterations. For the remaining 31 days of hospitalization, the patient received 0.75 grain of thyroid daily without the return of her former untoward responses and with an improvement in the myxedematous state. At the time of discharge to the clinic, she was more alert, her voice normal, and her skin of good texture, although still somewhat dry. Her basal metabolic rate was minus 14 per cent; her pulse rate, 62; the blood cholesterol, 280 mg. per 100 cc., with 66 per cent esters; her circulation time, 16 seconds; and her capillary permeability, within normal limits (fig. 3). All of her myxedematous signs and symptoms eventually disappeared while using 2.5 grains of desiccated thyroid substance daily, but such a dose was not tolerated until she had been under treatment in the clinic for a period of three months following her hospitalization. At the end of that time her blood cholesterol was 200 mg. per 100 cc. of blood; her basal metabolic rate, minus 6 per cent; and her pulse rate, 76. Her weight had decreased to 165 pounds.

Case No. 24, M. F., a 52-year-old, colored woman, was admitted to the hospital for weakness, malaise, nocturnal and exertional dyspnea, occipital headaches, constipation, and recurrent mild edema of the ankles. She had not felt entirely well since a thyroidectomy nine years previously, shortly following which the weakness and constipation had appeared. Her other complaints had been intermittently present for one year, except for the slight pretibial and ankle edema which had been noticed only during the month prior to admission. The patient was known to have been a hypertensive for many years. A hysterectomy had been performed for "fibroids" three years before admission. No relevant family history could be elicited. The patient was 65.5 inches tall, weighed 142.5 pounds answered questions sluggishly in a somewhat low-pitched, husky voice, and was in no acute distress. Her hair was dry and coarse; her face and eyelids, puffy and somewhat mask-like; her skin, thickened and dry. Her neck showed a well-healed thyroidectomy scar. It was difficult to make out any thyroid tissue on palpation. There was some tortuosity of the fundal blood vessels and thickening of the radial arteries on palpation. The heart was enlarged to the right and to the left. The apex impulse was forceful, in the sixth left interspace 3 cm. outside the midclavicular line. There was a loud systolic murmur heard over the entire precordium; the aortic second sound was accentuated with a ringing quality. The apical pulse was 52 per minute; the blood pressure, 160/110. No pulmonary abnormality could be detected. Her vocal cords moved normally. The abdomen showed some gaseous distension, but was soft; no organs or masses could be palpated. There was no pitting edema.

On admission her basal metabolic rate was minus 23 per cent. The circulation time (fluorescein, arm to lip) was 22 seconds. There were 4,200,000 red blood cells and 5,950 leucocytes per cu. mm.; of the latter, 40 per cent were lymphocytes. The hemoglobin was 80 per cent. Blood-sugar levels in mg. per 100 cc. at one-half, one, one-and-a-half, two, and three hours following the oral ingestion of 100 gm. of glucose were 95, 105, 160, 150, 115, and 120, respectively; no sugar appeared in the urine. The total blood-serum protein was 7.1 per cent, of which albumin comprised 3.2 per cent, with an albumin-globulin ratio of 0.95. The blood cholesterol was 340 mg. per 100 cc., and the esters, 240 mg. per 100 cc.

An electrocardiographic tracing (fig. 5) showed a

sinus bradycardia, a low voltage of all complexes, and a slightly prolonged P-R interval (0.51 seconds). A two-meter roentgenogram of the heart and lungs revealed a moderate increase in the bronchial markings throughout both lung fields. The cardiac shadow was markedly enlarged toward the left and moderately increased to the right. There was widening at the base and straightening of the left cardiac border.

Diagnosis: Myxedema with "myxedema heart"; generalized arteriosclerosis with hypertension and cardio-vascular disease; mild right and left heart failure.

Course in the hospital. Portions of the patient's record are graphically summarized in figures 1A and B. She has been continuously observed for 27 months. The severity of her cardiac findings was not fully appreciated on admission, and 0.5 grain of desiccated thyroid substance was given daily for 18 days, and then increased to 1 grain. Following this, she became severely decompensated with evidences of right-sided and left-sided involvement, massive ascites, peripheral edema, and a pulse rate of 90. Her cardiac condition was controlled by reducing the dose of thyroid to 0.5 grain daily, by the administration of 3 grains digitalis daily, and by the use of three doses of mercupurin solution, 2 cc. each, at five-day intervals. The patient remained free of cardiac symptoms on 1.5 grains of digitalis and 0.5 grain of thyroid daily. She promptly went back into failure when the digitalis was stopped and 1.5 grains of desiccated thyroid substance was given daily. This manifestation was slowly controlled by the cessation of all therapy. However, slight signs of myxedema reappeared 16 days later.

Serial examinations at intervals varying from one to four weeks have been made throughout her hospital stay in regard to the basal metabolic rate, the circulation time, the total and ester cholesterol, the serum protein, and protein partition. The total cholesterol has followed her thyroid status closely, apparently uninfluenced by the cardiac condition. Her ester percentage was a low normal (66%) during her first severe episode of cardiac failure, but at all other times has been well maintained in relation to the total value. Her basal metabolic rate and circulation time were diversely influenced by the myxedema on the one hand and cardiac failure on the other. For the same reason, fluctuations in weight were not indicative of a change in either condition.

The patient has been allowed to develop cardiac decompensation and myxedema separately or together on a number of occasions in an effort to establish accurately the influence of one upon the other and of cardiac and thyroid respectively upon both. The degree of myxedema was not influenced by cardiac failure, but the severity of cardiac failure was invariably greater if a period of myxedema preceded it. All factors relating to her cardiac condition and to her thyroid status are now satisfactorily controlled by 1.5 grains of powdered digitalis leaf and 1 grain of desiccated thyroid substance daily.

SUMMARY AND CONCLUSIONS

Cardiac complications have been observed in 20 of 24 patients with myxedema.

Thirteen of these patients were treated with desiccated thyroid and necessary supportive cardiac therapy. Seven of these were relieved of their thyroid insufficiency while under observation.

The influence of treatment for these individuals is discussed in relation to serial observations of the body weight, pulse rate, basal metabolism, circulation time, blood cholesterol capillary permeability, electrocardiogram, and roentgenogram of the heart and lungs.

The weight, pulse rate, basal metabolism, and circulation time were of little value in determining treatment when myxedema and cardiac failure were simultaneously present.

Capillary permeability (fluorescein method) was always increased in myxedema and was not influenced by cardiac failure. A decrease toward normal was a constant and early sign of improvement in the thyroid status.

Changes in total blood cholesterol were of importance in relation to the initial value. A decrease accompanied improvement of the myxedema, and high values were never seen in the adequately treated patient. Cardiac complications did not apparently alter the blood cholesterol.

In the electrocardiogram, a lowered voltage of all complexes in each of the three limb leads was the most constant accompaniment of the myxedematous state. This change was not dependent upon the presence of hydropericardium.

Roentgenography was of little value in directing the treatment of myxedema with cardiac complications.

Two cases of myxedema with cardiac complications are reported in detail.

Satisfactory initial doses of thyroid have ranged from 0.05 grain to 3 grains daily, with the majority of patients tolerating 0.25 grain without untoward symptoms.

Daily maintenance doses of desiccated thyroid have varied from 1.0 to 3.0 grains.

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Observations on Diseases of the Thyroid as Encountered in Western North Carolina

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THE THYROID gland is unique in that the incidence of various forms of disease of this gland differs markedly in different localities. The lability of the thyroid in response to a variety of stimuli, particularly to the amount of iodine available to the organism, results in variations in the size and histological structure of the gland which in turn lead to distinctive pathological variations in disease. Although many reports are extant as to the incidence of various forms of thyroid disease in the urban centers of the Atlantic Coast and in the recognized goitrous regions of the Great Lakes, mid-Western Plains and the Northwest, there is little reference in the literature to thyroid disease as it occurs in the Blue Ridge Mountains of the Appalachian Range. This mountainous area is a typical goitrous region and gives rise to a moderately high incidence of goiter. We thought it of interest, therefore, to analyze the incidence of various forms of disease of the thyroid gland in this area and compare it with similar tabulations based on observations in other areas.

INCIDENCE

During the two-year period from January 1, 1942 to December 31, 1943, a total of 298 patients were encountered at the North Carolina Baptist Hospital with some form of thyroid disease. During this same period a total of 5000 adult patients were studied in the medical and surgical divisions of this hospital, giving an incidence of approximately six per cent for the prevalence of thyroid disease of sufficient severity to warrant hospitalization. This is approximately six times as great as in a comparable group of hospital admissions in the Johns Hopkins Hospital where the incidence was approximately one per cent (1). The greater incidence of thyroid disease in the North Carolina institution is due to the fact that many of the patients were inhabitants of the endemic goitrous region of the Appalachian Mountains and its eastern plateau.

CLASSIFICATION

The satisfactory classification of goiter presents many difficulties, since there is often no correlation between the clinical criteria and the pathological findings, nor indeed, any agreement as to the fundamental nature of the abnormal process involved in some forms of thyroid disease. The above table summarizes the incidence of the conventionally recognized forms of the disease. In many cases the clinical im-

THE INCIDENCE OF VARIOUS TYPES OF THYROID DISEASE ENCOUNTERED AMONG 5,000 PATIENTS IN THE NORTH CAROLINA BAPTIST HOSPITAL

	Males	Females	Total
Diffuse Colloid (simple) Goiter	2	50	52
Nodular Non-toxic Goiter (including colloid and adenomatous nodules)	13	80	93
Toxic Adenoma (nodular and diffuse)	8	78	86
Exophthalmic Goiter (Graves' disease)	3	21	24
Carcinoma	1	5	6
Acute Thyroiditis	1	1	2
Chronic Thyroiditis			
Riedel's struma	0	2	2
Struma lymphomatosa (Hashimoto)	0	7	7
Hypothyroidism	4	22	26
TOTAL	32	266	298

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pression differed markedly from the findings on examination of the microscopic sections. The classification as given in the table is based on the final pathological diagnosis rather than on the clinical diagnosis, when the two are in disagreement.

Non-toxic goiter. A total of 145 patients, or approximately half of our series, suffered from some form of non-toxic goiter, that is, were free of any evidence of thyrotoxicosis. Of these, 52 —one sixth of the total—had a symmetrical, diffusely enlarged thyroid (colloid or simple goiter). The other 93 had some form of non-toxic nodular goiter. This purely anatomical and clinical classification includes not only the goiters in which nodule formation is due to localized areas of hyperinvolution in a colloid goiter with the formation of a pseudo-capsule but also true adenomatous nodules. It is impossible to differentiate these clinically; and even the criteria for their differentiation pathologically are not entirely satisfactory.

The high incidence of non-toxic, diffuse and nodular goiter in our series reflects the fact that the hospital population is derived in large part from an endemically goitrous area.

Toxic goiter. Eighty-six patients were found to be suffering from thyrotoxicosis with a nodular or diffuse adenoma. The term "adenomatous" is often used synonymously with "nodular" but this is incorrect. Although most toxic adenomas are encountered in nodular goiters, there are instances in which the typical clinical and pathological findings of toxic adenoma are due to a diffusely enlarged gland.

The high incidence of toxic adenoma (29 per cent of 298 goitrous patients) is worthy of note. On the other hand, there were only 25 patients with classical Graves' disease, an incidence of 0.5 per cent (of 5000 hospitalized patients), which is less than that seen in populous urban areas. Over three and one-half times as many patients with toxic adenoma were encountered as with Graves' disease. This is in contrast to their relative frequency in non-goitrous areas where the incidence of the latter is several times that of the former (2, 3). This discrepancy speaks for a different etiology for the two types of thyrotoxicosis and suggests that endemic goiter plays an important role in the evolution of toxic adenoma.

Carcinoma. Despite the frequency of nodular goiter of the colloid and adenomatous types, the relative infrequency of carcinoma of the thyroid should be emphasized. Less than 2 per cent of the goiters encountered were malignant. Although all of these originated in a nodular goiter the results fail to support the claim that as many as 6 to 10 per cent of all nodular goiters assume malignant characteristics (4). The incidence of carcinoma in our series is approximately that noted by others in non-goitrous areas (3, 5).

The ages of the patients in whom carcinoma was found are of interest. Two of them were only 27 years of age; the others ranged from 44 to 76 years, with an average age of 47 in all patients. In one instance the goiter had first been noted 6 years previously; in the others, it had been present for a period of 15 to 20 years. Histologically all of the tumors, except one, were papillary adenocarcinomas of low-grade malignancy.

Thyroiditis. The occurrence of 9 instances of chronic thyroiditis (Riedel's struma and Hashimoto's disease) is contrary to the general belief that these conditions are very rare (6). More attention should be given to these conditions, for, in spite of the fact that the clinical findings were pathognomonic of these forms of goiter, in none of these patients was the diagnosis suspected before operation.

Of particular interest was one patient (age 30) in whom the gland showed the existence of the characteristic findings of both Riedel's struma and Hashimoto's disease in contiguous areas. Unless one assumes the coincidental occurrence of both diseases in the same patient this finding would favor the contention that Riedel's struma is merely a later stage of development of struma lymphomatosa (Hashimoto), as first suggested by Ewing (7) and accepted by most subsequent authors (8). Some have objected to this view on the ground that Hashimoto's disease is encountered almost entirely in women over 45 years of age, whereas Riedel's struma may occur at any age and in both sexes (9). However, this contention is not in accord with the findings in our patients with Hashimoto's disease for their ages were 25, 30, 31, 34, 35, 45, 46 and 48 years, respectively—an average of 37 years. This contrasts with an

average age of 49 years in fifty patients collected by Graham (9) and McClintock and Wright (10).

No cases of syphilis, tuberculosis or other chronic infections of the thyroid were seen, attesting to the relative infrequency of these disorders (1, 11).

Hypothyroidism. Hypothyroidism was diagnosed clinically with much greater frequency than is indicated in the accompanying table. However, we have excluded from the tabulation all cases in which the evidence for the existence of this disorder was obviously incomplete. Thus, patients in whom the diagnosis of hypothyroidism was based on an abnormally low basal metabolic rate without other characteristic findings of thyroid deficiency are excluded since this condition is not uncommon in normal individuals.

Since our study was confined to adults, cretinism and juvenile hypothyroidism are not included in the table. The former is relatively rare but the latter condition was observed frequently in children whose principal complaint was retardation of growth. This was accompanied by retarded mental development and the typical roentgenologic findings characteristic of juvenile hypothyroidism.

THE EFFECT OF ADMINISTERING IODINE IN TOXIC ADENOMA

The effectiveness of iodine in lowering the basal metabolic rate and ameliorating the symptoms of exophthalmic goiter is generally accepted. The effect of iodine in the thyrotoxicosis induced by a toxic adenoma is, on the other hand, still a matter of controversy. Many believe that there exists no essential difference in the reaction of these two conditions to iodine and advocate the routine use of the drug preoperatively in both forms of goiter. Thus Cutler and Graham (12) found that improvement was the rule following the administration of iodine in toxic adenoma and that there was an appreciable recession of the basal metabolic rate following its use. Others believe that the effect of iodine in toxic adenoma is slight and that, although it may at times cause some remission in the symptoms, its effect is not striking. Thus, Goetsch (2) considers the remission sometimes seen in adenoma following the use of iodine to indicate the presence in the thyroid of hyperplastic cellular elements comparable to those occurring in Graves' disease. Unquestionably the reaction of patients with toxic adenoma to iodine varies, due perhaps to a difference in the etiological factors responsible for the basic disorder in the thyroid. It is of interest, therefore, to consider the reaction of the patients in our series to the administration of iodine.

The basal metabolic rate in the patients with toxic adenoma of our series varied from +10 to +63 per cent, with an average of +34 per cent. Following the administration of Lugol's solution pre-operatively, the basal metabolic rate varied from +6 to +78 per cent, with an average of +28 per cent. If one considers the effect of bed-rest and hospitalization on the basal metabolic rate, this reduction is of questionable significance and demonstrates that, on the whole, iodine fails to reduce the basal metabolic rate in toxic adenoma as it does in Graves' disease. Analyzing the data further it was found that: in 7 per cent of the patients the basal metabolic rate was increased more than 10 per cent by the administration of iodine; in 43 per cent, the basal metabolic rate was decreased more than 10 per cent; and in 50 per cent, the basal metabolic rate was altered less than 10 per cent by the administration of iodine.

The conclusion that iodine does not exert the same effects in toxic adenoma that it does in Graves' disease is of considerable importance. It is evidence for the view elaborated elsewhere (1) that the disturbance in Graves' disease and in toxic adenoma differs fundamentally. The basic disturbance in the former is not in the thyroid gland which merely reacts with hyperfunction to a disturbance elsewhere in the organism (possibly in the vegetative nervous system). In toxic adenoma, on the other hand, the disturbance is primarily in the thyroid.[2] This interpretation would explain why iodine, which pharmacodynamically is a mild stimulant of thyroid activity (1), has little or no action on the adenomatous gland and may even increase

[2] The term, "primary hyperthyroidism," suggested as a synonym for Graves' disease is, according to this view, a misnomer. Toxic adenoma is more correctly designated as primary and Graves' disease as secondary hyperthyroidism.

the activity of it. In Graves' disease, on the other hand, it may be assumed that the main site of action of iodine is extra-thyroidal, probably on the nervous system.

SUMMARY

Approximately 300 cases of thyroid disease encountered among 5,000 patients in an endemic goitrous area of North Carolina, were analyzed. The striking difference between the types of hyperthyroidism found in such an area as compared to the series reported from non-goitrous regions is indicated and the implications of the difference are discussed.

The difference in the reaction to iodine of patients with toxic adenoma as compared to those suffering from Graves' disease is emphasized. The bearing of this fact on the etiology of these two forms of thyrotoxicosis and on the mechanism of action of iodine in thyroid disease is considered.

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The Use of Thiourocil in Thyrotoxicosis

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SEVERAL recent reports (1–5) attest to the usefulness of thiouracil in the treatment of various forms of thyrotoxicosis. Details concerning its administration and effectiveness have been described in sufficient detail to preclude the necessity of their recapitulation here. We wish merely to point out several aspects concerning the use of this drug which have not been stressed by previous workers.

We have used thiouracil[2] in a total of 18 patients with results comparable to those obtained by previous workers. The drug was administered in doses of 0.1 gm. six times daily. The principal toxic effect which we have observed has been an urticarial eruption which appeared in 4 of the patients two to three days after beginning the administration of the drug but which in no case was sufficiently severe to necessitate withdrawal of the drug. In 4 of the patients there was also a drop in the leucocyte count from a normal level of 6,000–10,000 to 3,000–4,000 on the third or fourth day after medication was begun. No further decline in the leucocyte count occurred when the dosage was then decreased to 0.4 gm. daily. We have followed the suggestions of previous workers by administering thiouracil in doses of 0.6 gm. for from three to seven days, depending upon the time of appearance of definite evidence of amelioration of symptoms. The dose was then reduced to 0.4 gm. for three to four days and then maintained at 0.3 gm. per day for a period not exceeding two weeks. In cases in which the drug was required for longer periods a dose of 0.1 to 0.2 gm. daily was administered. A satisfactory response was obtained in all patients except one in whom the drug was given in doses of 0.6 gm. daily for a period of three weeks. This patient was admitted to the hospital in a thyroid storm and had been treated with Lugol's solution prior to the administration of thiouracil. She had a large nodular goiter of 20 years' duration which had begun to give evidence of toxicity about two years prior to admission to the hospital. The patient had failed to improve under iodine therapy and no improvement was noted during the three weeks that she received thiouracil.

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EXOPHTHALMIC GOITER

The effectiveness of thiouracil in causing a remission of the acute symptoms of Graves' disease suggested a combination of this therapy with irradiation of the gland as a substitute for the usual procedure of administration of iodine followed by thyroidectomy. Although many have advocated irradiation by x-rays as a substitute for surgery in exophthalmic goiter there are numerous objections to the use of this procedure (6). The fact that considerable time must elapse before irradiation will effectively inhibit the activity of the thyroid militates strongly against its use. However, with the availability of thiouracil as a means of inducing a temporary remission, it was thought that a combination of this medicament with irradiation might be safely used in the treatment of exophthalmic goiter, particularly in younger patients and in those cases in which exophthalmos is prominent and there is danger of malignant exophthalmos following surgical removal (7). We have treated two patients in this manner with very satisfactory results in both. The following case report is illustrative of the effects obtained.

CASE REPORT

A 15-year-old girl with a diagnosis of exophthalmic goiter was referred to the hospital for operation. The patient was a well-developed, young woman who had

the obvious facies and manifestations of Graves' disease. There was marked nervousness, emotional instability, tachycardia (pulse rate at rest, 110) marked exophthalmos, positive Dalrymple's, von Gräfe's, Stellwag's, and Möbius' signs. The thyroid was diffusely enlarged. There was a fine, constant tremor of the outstretched hands. The biceps, triceps and patellar reflexes were all hyperactive. The heart sounds were loud and snapping; the blood pressure was 140/80. The basal metabolic rate on two occasions was +30 and +35 per cent. Other symptoms of complaint were marked irritability, purposeless movements, hyperhydrosis, abnormal sensitivity to heat, diarrhea, a voracious appetite, a sense of weakness of the voluntary muscles and psychic instability with a tendency towards emotional outbursts.

The patient was given 0.6 gm. of thiouracil[2] daily for five days. She was confined to bed and given multiple, high-carbohydrate, high-protein feedings. The only other medication was thiamin hydrochloride in 10 mg. doses three times daily. After five days a marked amelioration in the symptoms was evident. The basal metabolic rate had decreased to +15 per cent. The leucocyte count, which prior to treatment was 6,750 (lymphocytes 42 per cent), had decreased by the fifth day to 3,200. The dosage of thiouracil was then decreased to 0.3 gm. daily, maintained at that level for one week, and subsequently reduced to 0.2 gm. daily, at which level it was maintained for the next 15 days. Two weeks after the beginning of treatment the basal metabolic rate was +3 per cent; one week later, −5 per cent; and at the end of one month, −15 per cent.[3] Subsequent determinations over a period of three months showed a basal metabolic rate which varied between −5 and −10 per cent.

Beginning on the seventh day following admission, the area over the thyroid was irradiated (by Dr. C. L. Gray) with 200 r through a single portal. This was repeated 4, 7 and 11 days later. A similar course of x-ray therapy was given twice subsequently at bi-weekly intervals.

The patient was discharged from the hospital 21 days after admission with complete remission. The case has been followed for a period of six months during which time there has been no recurrence of the symptoms.

TOXIC ADENOMA

As shown in another paper (8) the reaction, of many patients with toxic adenoma to the pre-operative treatment with iodine is far from satisfactory. For this reason we have given thiouracil as a substitute for iodine in 12 cases of toxic adenoma with results which, in our opinion, are superior to those seen following the use of iodine. Sedatives, a high caloric diet and the other routine procedures, as well as digitalis, when indicated, were also used. A single case report will be cited as illustrative of the results obtained.

[3] The marked reduction below normal of the basal metabolic rate in patients receiving thiouracil is attributable to the depressing effect of the drug on oxidative processes of the tissues generally in addition to its specific action on the thyroid gland.

CASE REPORT

A 72-year-old woman was admitted to the hospital with the typical findings of thyrotoxic heart disease. She had an enlarged nodular goiter which had been present for eight years. Her principal complaints on admission were extreme nervousness, weight loss, palpitation and weakness. The physical examination revealed evidence of recent weight loss, a skin of very fine texture, marked tremor of the outstretched hands, hyperactive reflexes and slight edema of the lower extremities. The heart was enlarged, with a totally irregular rhythm, the rate being 140 at the apex with a pulse deficit of 40 at the wrist. An electrocardiogram confirmed the existence of auricular fibrillation. The basal metabolic rate was +20 per cent.

The patient was digitalized and 0.6 gm. of thiouracil was administered daily. At the end of the week there was marked subjective improvement and the dose of thiouracil was reduced to 0.4 gm. daily. The basal metabolic rate on the 10th day was +7 per cent. The patient was subjected to a sub-total thyroidectomy two weeks after admission and was discharged five days later in excellent condition. The administration of thiouracil was discontinued on the day of operation.

"MASKED" HYPERTHYROIDISM

In addition to its use instead of iodine for the pre-operative treatment of toxic adenoma, thiouracil has also proved valuable in our hands as a means of determining by therapeutic test the presence of thyrotoxicosis in the so-called cases of "apathetic" or "masked" hyperthyroidism in which the evidence for the existence of a thyrotoxic state, although suspected, was not sufficient to warrant surgical interference. The difficulty of proving the existence of thyrotoxicosis in such patients is well known for they often present an atypical clinical picture of some other type of disease, such as organic heart failure, diabetes mellitus, gastro-intestinal disorders or psychoneurosis (8). Even when certain suggestive signs and symptoms such as persistent moderate tachycardia, weight loss, or an increased basal metabolic rate exist, difficulty in diagnosis may occur, particularly in cases in which the presence of a definite nodular goiter can not be demonstrated clinically. As an illustration of the usefulness of thiouracil in such conditions, the following case report may be cited.

CASE REPORT

A 49-year-old farmer entered the hospital complaining of dyspnea and swelling of the lower extremities. He had first noticed dyspnea on exertion about two years previously but this had become progressively more marked during the preceding year. There had also been, during this time, increasingly frequent attacks of nocturnal dyspnea. About six weeks prior to admission he first noticed swelling of the legs and abdomen. For the preceding three weeks he had been expectorating frothy, bloody, mucoid material. He had also noticed increasing nervousness and instability. Despite a good appetite there had been a considerable loss of weight, but during the weeks preceding admission the appetite had become poor. He had been treated by his local physician with digitalis, with an apparent worsening of his condition.

Of significance in the past history were attacks of rheumatism at the ages of 16 and 20. The physical examination revealed an obviously dyspneic, edematous, orthopneic, somewhat cyanotic man with a slight icteric tinge of the skin and sclerae and slight cyanosis of the lips. The point of maximum impulse of the heart was neither seen nor felt. The heart was moderately enlarged to percussion. The heart sounds were faint. There was a moderately rough systolic murmur at the apex and also one at the base. No diastolic murmurs were heard. The rhythm was totally irregular. The blood pressure was 140/85. There was dullness at the left base posteriorly, with diminished breath sounds and scattered râles. There was marked edema of the legs and a moderate degree of ascites.

The laboratory examination revealed hypo-proteinemia which was thought to be secondary to early hepatic insufficiency and to be a contributing factor to the edema and ascites.

A consulting cardiologist suggested that the cardiac failure was probably due to mitral stenosis and that a diastolic murmur was not heard because of the presence of auricular fibrillation. However, he was unwilling to make a decision as to the presence or absence of thyrotoxicosis.

The patient was treated by the usual procedures for congestive failure, including digitalis, diuretics and a Karell regimen. However, he cooperated poorly and left the hospital against advice on the fourteenth day after admission, without noticeable improvement. The patient returned to the hospital on three subsequent occasions during the succeeding year; each time the findings were essentially as described above. He had been bed-ridden throughout this period and received various forms of medication, including iodine, digitalis, and diuretics without improvement.

The patient was readmitted to the hospital for the fourth time one year following his first admission. His basal metabolic rate was now +35 and +30 per cent on successive days. The blood-cholesterol level was 110 mg. per 100 cc. At this time thiouracil was first administered in daily doses of 0.6 gm. After one week on this medication his basal metabolic rate had dropped to +8 per cent and for the first time there was a marked improvement both in the subjective and objective findings. There was a marked change in the patient's mental attitude. Contrary to his previous behaviour, he was now cooperative. Two weeks following admission the blood cholesterol had risen to 174 mg. per 100 cc. and the basal metabolic rate decreased to −7 per cent. The pulse rate was 72. The edema and ascites gradually disappeared and he was subjected to a subtotal thyroidectomy three weeks after entering the hospital.

The specimen removed at operation consisted of two well-encapsulated fragments of thyroid tissue, representing the major portion of both lateral lobes plus the isthmus, and weighed 36.5 gm. Sections of this tissue on microscopic examination revealed diffuse hyperplasia of the acini with evidence of involution.

The patient had an uncomplicated post-operative course and was discharged greatly improved on the tenth post-operative day. He was seen again one month later, at which time he had returned to active, manual labor. No evidence of heart failure was now present. The basal metabolic rate was −2 per cent; the pulse rate, 63; the cholesterol level of the blood, 224 mg. per 100 cc.

SUMMARY

Thiouracil was used in the treatment of 18 patients manifesting various forms of thyrotoxicosis. In the treatment of Graves' disease in young adults, it was used in combination with x-ray irradiation of the thyroid. Thiouracil was found to be superior to iodine in the pre-operative preparation of patients with toxic adenoma. The drug was also used to advantage as a therapeutic test in the diagnosis of questionable "masked" hyperthyroidism. Typical case reports illustrative of the response to this form of therapy are given.

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Non-diabetic Glycosuria with Comments Concerning the Significance of Insulin-Induced Ketonuria: A Case Report

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CASE REPORT

A 24-YEAR-OLD soldier had completed three years of high school; his civil occupation was that of a plumber. The patient's past history was irrelevant and the family history disclosed no evidence of any familial diatheses, including diabetes mellitus.

The patient first came under observation July 6, 1942 at another hospital because of an upper respiratory infection. The admission urine specimen contained sugar and subsequent urinalyses confirmed this finding. Following the discovery of glycosuria the patient, on direct questioning, admitted that polyuria, polydipsia and polyphagia had been present for an unknown period of time. The acute nasopharyngitis subsided promptly. The patient was placed on a restricted carbohydrate diet divided into four meals and received regular insulin in 5-unit doses before each meal. Subsequent examinations of the urine showed fewer specimens positive for sugar.

After a month of hospitalization, the patient was returned to his former duties. He was instructed to follow an unmeasured diet with carbohydrates curtailed and divided into three meals. He was also advised to examine his urine before each meal and to make adjustments in his insulin dosage according to the color reaction of the Benedict test. Because of the change from four meals a day to three, the patient was told to modify a basic dosage of insulin, units 10, before each meal in the manner described.

On this regimen, the patient remained on duty but rapidly reduced his breakfast insulin to zero because his early morning specimens were invariably sugar-free. He noted periodic nervousness an hour after lunch and supper and found that this was relieved by reducing his insulin to 5 units before these meals. He continued on this regimen until May, 1943 at which time he complained of feeling listless upon arising and frequently had early morning headaches. On May 6, 1943 the fasting blood sugar was 45 mg. per 100 cc. of blood[1] and the urine, although negative for sugar, showed a trace of acetone. The patient was advised by the station dispensary physician to take insulin, units 5, before breakfast. His early morning complaints continued and on May 30, 1943 the fasting blood sugar was 65 mg. per 100 cc. of blood[1] and the urine again showed no sugar but a trace of acetone.

Early in June, 1943 the patient contracted acute gonococcal urethritis and because of his known previous diagnosis of diabetes mellitus he was re-hospitalized at his station. The gonorrheal infection was treated with sulfathiazole and throughout this period of treatment he received an unmeasured restricted carbohydrate diet divided into three meals. He was given insulin varying in dosage from 5 to 10 units before each meal. The gonorrhea was considered sulfonamide-resistant and the patient was transferred to this hospital.

The patient was admitted to the genitourinary service where initial smears and later provocative measures failed to show the presence of gonococci in the urethral discharge. In view of the alleged diabetes I was asked to see the patient.

[1] Presumably venous blood sugar determinations by the older Folin-Wu technique.

The urine on first examination showed less than 1% sugar and no acetone or diacetic acid. The patient was ambulatory and seemed quite well. The physical findings were entirely normal. A diet of three approximately equicaloric meals totaling Carbohydrate, 250 gm.; Protein, 80 gm.; Fat, 60 gm.; was ordered. Twenty-four-hour urine summaries were collected and preserved with toluene. Each summary was started after the first voiding upon arising. All voidings, including the first specimen passed on arising the following day, constituted each summary. In this way the summaries represented all dextrose lost from the previous day's meals. The first few days the total urinary output varied between 3 and 4 litres and then gradually decreased to from 1.8 to 2.4 litres per twenty-four hours. Quantitative studies showed ¼% to traces of dextrose and a total daily dextrose loss of less than 10 gm. The urines were consistently free of ketones. The patient was allowed to stabilize for twelve days on the diet mentioned. During the stabilization period all complaints of nervousness, listlessness and headaches in the morning disappeared. At this time a carbohydrate-tolerance test, using 100 gm. dextrose, was made with the following results:

Time	*Blood Sugar*[2]	*Urine Sugar*
Fasting	114 mg./100 c.c.	0
½ hour	167 mg./100 c.c.	trace[3]
1 hour	145 mg./100 c.c.	trace
2 hours	130 mg./100 c.c.	trace
3 hours	92 mg./100 c.c.	0

[2] Capillary blood sugar determinations by the Folin Micromethod.
[3] Less than ¼%. Method: see ref. 5.

Liver function studies consisting of bromsulfalein disappearance time and intravenous hippuric acid excretion showed no abnormality in liver function. The diagnosis of renal glycosuria was then made. The patient was advised of the benign nature of his difficulty and was instructed not to take insulin unless future studies proved the need for it.

COMMENT

The medical cliché, "Fats burn in the fire of carbohydrates," too frequently colors the interpretation of *any* ketonuria. That the case reported is from military records is incidental and does not reflect criticism upon medical officers. The case also illustrates the tendency of clinicians to consider glycosuria and diabetes mellitus as synonymous. Mirsky (1) recently mentioned this fact in introducing his discussion of the significance of glycosuria. Obviously the diagnosis of diabetes mellitus on the basis of glycosuria alone is not tenable. The evaluation of the significance of glycosuria, as pointed out by Mirsky, depends on three factors: (a) the concentration of dextrose in the arterial blood supply of the glomeruli, (b) the rate at which the glomeruli filter dextrose out of the blood, and (c) the rate at which destrose filtered out by the glomeruli is reabsorbed by the tubules. Arterial blood-sugar determinations and especially the information to be derived from any of the standard methods of determining carbohydrate tolerance are readily available to the clinician. These studies should constitute the minimal investigation in all cases of glycosuria.

The significance of acetone in urine specimens collected at times when the blood sugar is found to be at hypoglycemic levels is generally neither understood nor appreciated. The repeated observations in the case described illustrate that erroneous interpretation of this phenomenon may lead to therapy that could be of serious consequence. In the light of newer concepts of carbohydrate and fat metabolism it is believed that such acetonuria reflects a state of depleted glycogen stores in the liver. The patient's long-standing complaints of morning listlessness and headaches are interpreted as resulting from recurrent nocturnal hypoglycemic states. With each hypoglycemic state there is an increase in hepatic glycogenolysis which leads to glycogen depletion. Under such conditions the fat and protein metabolism within the liver is increased and there is a consequent increase in ketone production. Peripheral ketone utilization remains unaffected and accordingly the increased ketonemia may bring about a clinical ketonuria. Restricted carbohydrate intake and the injudicious use of insulin may produce acetonuria by this mechanism as has been shown by Somogyi (2). It is therefore observed that the use of insulin upon encountering acetone in a sugar-free urine specimen is not necessarily indicated and may, indeed, be definitely contra-indicated. The pa-

tient's subsequent progress without symptoms and without insulin and with a liberal dietary carbohydrate allowance substantiates the validity of this line of reasoning. The views expressed are based on some of the recent work of Somogyi (3, 4).

The estimation of current insulin needs should not routinely be made on the basis of the degree of glycosuria in isolated urine specimens voided before each meal. The use of the qualitative Benedict or Fehling tests for such a procedure warrants comment. It has been my experience that most confusion with regard to "scientifically guessing" the insulin need occurs when the urine reaction is 4 plus (brick red) with these tests. The 4-plus (brick red color) reaction may denote glycosuria varying from 1% to 6% or more. Similar difficulties, though less striking, occur with the lesser reactions of the qualitative tests. These difficulties led to the adoption of Somogyi's (5) rapid method for the quantitative estimation of urine sugar. This method is as rapid as the qualitative tests, requires little more in the way of equipment and is extraordinarily accurate. This method was used in the quantitative determinations of the glycosuria in the 24-hour specimens in the case reported.

CONCLUSION

It is to be emphasized that when the diagnosis of diabetes mellitus has been suspected but not proven, there is no need for haste in using insulin, when the patient is free of symptoms, has been maintaining body weight and does not show ketonuria. It is of greater benefit to the patient to go back to an early principle set forth by Naunyn. This principle consists of determining the carbohydrate balance by giving a measured diet and estimating the loss of dextrose in the sugar day by day. Even when blood sugar studies are not available, such an approach applied to any case of glycosuria will give a more accurate reflection of the severity or mildness of the condition at hand.

SUMMARY

The case is reported of a 24-year-old soldier in whom recurrent glycosuria led to an erroneous diagnosis of diabetes mellitus. Inappropriate treatment with insulin resulted in headaches and lassitude. Blood-sugar and carbohydrate-tolerance studies should always be made in such cases.

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The Effect in Man of Chronic Intermittent Anoxia on Glucose Tolerance and the Urinary Excretion of Sodium, Potassium, Chloride, Phosophorus, Nitrogen, and 17-Ketosteroids[1]

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The experiments reported in this paper were designed to test the hypothesis that chronic intermittent anoxia acts in man as a stimulus to the adrenal cortex, producing effects similar to those described by others in laboratory animals under conditions of relatively acute anoxia. For this purpose we studied *a*) the urinary excretion of sodium, potassium, chloride, phosphorus, nitrogen and 17-ketosteroids, and *b*) the glucose tolerance in human subjects exposed to low pressures in a decompression chamber.

Table 1. Diet of *J.P.—11,500 Feet*

Carbohydrate	290 gms.
Protein	128 gms.
Fat	165 gms.
Calories	3157

Daily Intake as Determined by Analyses. See Table 5.

In a series of well-known experiments, Evans (1, 2) observed a remarkable increase in the blood sugar and liver glycogen of rats exposed to half atmospheric pressure. These and other effects of acute anoxia on carbohydrate metabolism were further studied by other investigators including Lewis and co-workers (3) and Langley and Clarke (4). The latter two groups of workers described in addition marked augmentation of the urinary excretion of sodium, potassium, chloride, phosphorus and nitrogen in dogs exposed to simulated altitudes of 18,000 to 20,000 feet. The changes in electrolyte excretion were found by Langley and Clarke to decrease with repeated exposure. The changes both in the carbohydrate metabolism and in the excretion of electrolytes and nitrogen were, with the exception of the potassium diuresis, abol-

Table 2. Diet of *R.D.—11,500 Feet.*

Carbohydrate	365 gms.
Protein	120 gms.
Fat	169 gms.
Calories	3461

Daily Intake as Determined by Analyses.

Day[1] of Experiment	Sodium gms./day	Chloride gms./day	Phosphorus gms./day	Nitrogen gms./day
9 C	4.14	6.84	2.34	20.3
16 E	4.05	6.92	2.29	20.5
2 R	4.07	6.79	2.30	20.7

[1] In this and the following tables the experimental day is assigned to one of three periods: control (C); experimental when subject was at altitude (E); and recovery (R). The lengths of the control periods are as follows: *J.P.—11,500 feet*, 14 days; *R.D.—11,500 feet*, 18 days; *W.H.—11,500 feet*, 9 days; *W.H.—16,600 feet*, 8 days; and *A.C.—18,000 feet*, 11 days. Thus, day 9 C for *R.D.* was 9 days before the first exposure to altitude.

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago. The manuscript was submitted to the Committee on Medical Research on September 27, 1943.

ished by adrenalectomy and restored by adequate replacement therapy. Thus the role of the adrenal in mediating certain effects of acute anoxia in the dog and rat was well established.

Lewis and co-workers (3) obtained less striking changes in the mineral metabolism of eight normal men exposed for five hours to a simulated altitude of 13,000 feet. There was no change in the excretion of sodium and potassium and a decrease in the excretion of chloride, phosphate and nitrogen. Observations on chronic intermittent anoxia in man were made by Armstrong (5) who noted an increase in urine volume at altitude (p. 284) and who suggested that the asthenia, fatigue and hypotension noted in aviators with long service resembles the clinical picture of mild adrenal cortical insufficiency (pp. 287–8).

We are not aware of any studies of the glucose tolerance of man under these conditions.

METHODS

Throughout the experiments our subjects lived in the metabolism ward of the hospital under the care of a dietitian and nurses carefully trained in the technic of metabolic-balance studies. The times of opening and closing the urine specimens and the collection of the stools were always supervised by a nurse or investigator. Determination of the creatinine excretion was used to check the completeness of all urine specimens and carmine was administered to mark off the stool collections.

The *diets* were prepared by the dietitian in the metabolism kitchen and were served either in the subject's room or in the decompression chamber. To obtain constancy of intake a number of precautions were taken. The subjects ate the same amounts of the same foods every day and all foods were purchased either in large lots or from sources offering a constant product. Sirloin butts large enough to last a subject three weeks were cut into steaks and frozen until ready to use. Canned vegetables, fruits and fruit juices were purchased in case lots. Bread was obtained from a commercial bakery daily and was always weighed in the same state of freshness. "Salt-free" butter was washed until the wash water gave no test for chlorides. The food was seasoned with a weighed amount of C. P. sodium chloride, and the subjects drank distilled water in amounts which, though unrestricted, were carefully measured. All food portions were weighed with an accuracy of 1 per cent and we insisted that

TABLE 3. DIET OF *W.H.—11,500 Feet* AND *16,606 Feet*

Carbohydrate	323 gms.
Protein	119 gms.
Fat	179 gms.
Calories	3379

Daily Intake as Determined by Analyses.
11,500 Foot Experiment see Table 6.
16,600 Foot Experiment:

Day[1] of Experiment	Sodium gms./day	Chloride gms./day	Phosphorus gms./day	Nitrogen gms./day
6 C	4.47	7.07	2.36	19.7
19 E	4.49	6.98	2.28	20.1
42 E	4.51	6.97	2.32	19.7

[1] See footnote, Table 2

TABLE 4. DIET OF *A.C.—18,000 Feet*

After Day 1 C[1]		After Day 6 E[1]	
Carbohydrate	425 gms.	Carbohydrate	425 gms.
Protein	127 gms.	Protein	127 gms.
Fat	198 gms.	Fat	173 gms.
Calories	3990	Calories	3755

Daily Intake as Determined by Analyses

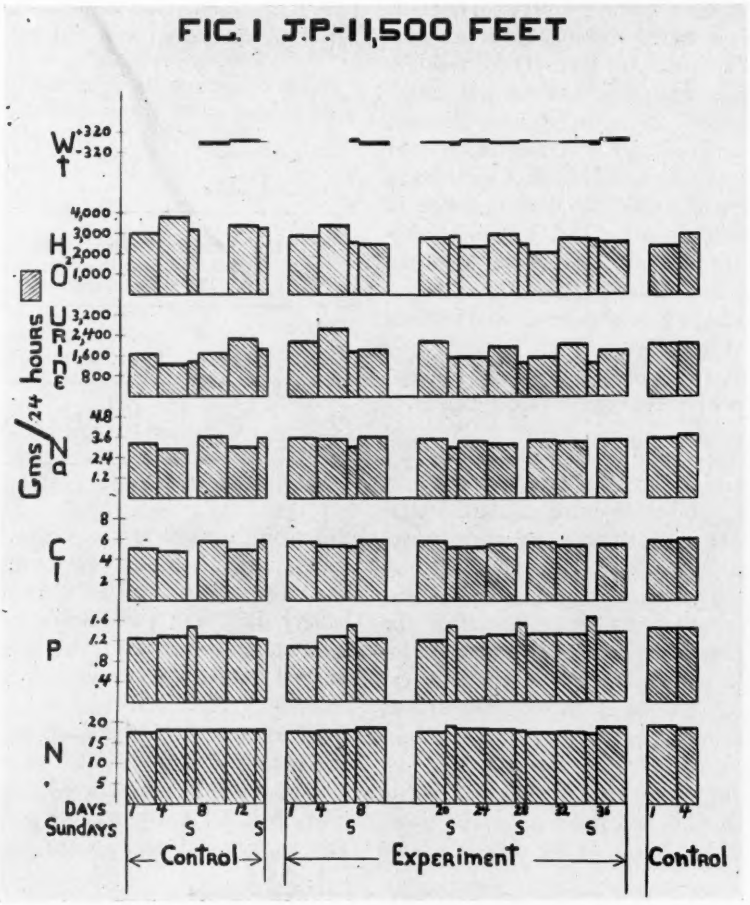
Day[1] of Experiment	Sodium gms./day	Chloride gms./day	Phosphorus gms./day	Calcium gms./day	Nitrogen gms./day
9 C	4.83	7.47	2.64	1.66	21.2
12 E	4.79	7.41	2.46	1.69	20.9
3 R	4.74	7.37	2.57	1.67	21.7

[1] See footnote, Table 2.

our subjects not only eat all their diet but lick their plates in addition.

At regular intervals an aliquot of all foods eaten, except butter, sugar and sodium chloride, was weighed in an evaporating dish and sent to the laboratory for analysis. Tables 1 to 4 give the composition of the diets and the results of the analyses of the food aliquots and demonstrate the constancy of intake of electrolytes and nitrogen throughout the experiments.

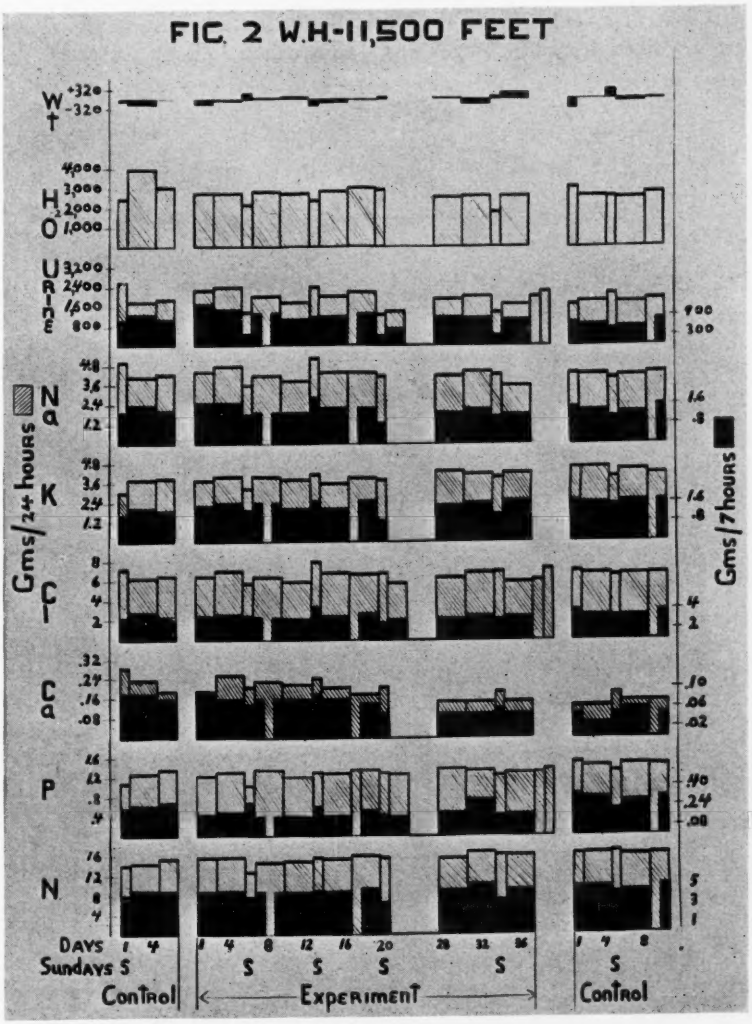
Weight balance. At the beginning and end of each metabolic period (usually of one to three days' duration) the nude weight of the subject before breakfast and after voiding was obtained in a chair balance with a sensitivity of 5 grams. Under the conditions of our experiment, with a constant diet and rather constant activity, providing the bowel habit was regular, the gain or loss in body weight (termed in this paper *weight balance*) is a close approximation of the water balance.



In Figures 1 to 5 the following abbreviations and symbols are used:

Wt. signifies Weight Balance
H_2O signifies Water Intake
Urine signifies Urine Volume
Na signifies urinary excretion of Sodium
K signifies urinary excretion of Potassium
Cl signifies urinary excretion of Chloride
Ca signifies urinary excretion of Calcium
P signifies urinary excretion of Phosphorus
N signifies urinary excretion of Nitrogen
S on the base line signifies Sunday

Water intake. Figures for water intake include only the drinking water and the volume of fruit juice, milk, coffee, etc., served on the tray. The water derived from the more solid foods was quite constant under the conditions of the experiments.



Glucose tolerance. Except in the case of *R. D.*, glucose-tolerance tests were carried out with the subjects in the fasting state. *R. D.* was in the chamber from 12:00 noon until 6:00 p.m. so that he was allowed his usual breakfast at 8:00 a.m., but was given no lunch until after the tolerance test. The same schedule was followed for the control tests as for those performed at altitude. In all subjects the glucose was administered approximately one hour after the beginning of exposure. The test meal consisted of 1 gram of glucose per kilogram of standard weight dissolved in 7 cc. of water for each gram of glucose and flavored with lemon juice.

CHEMICAL METHODS

The food and stool specimens were dried, ground and sieved before sampling. The urine was kept in a refrigerator and sufficient sul-

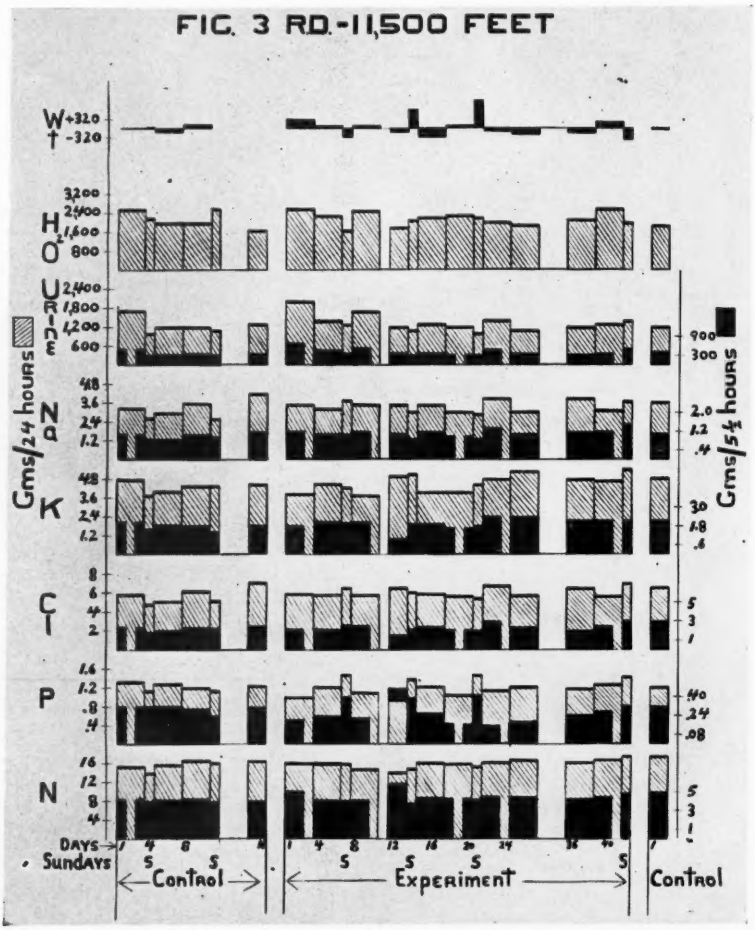
furic acid was added to prevent the loss of ammonia.

Chloride in the urine was determined by the Volhard-Harvey titration as described by Peters and Van Slyke (6) (p. 833). The dried food and stools were analyzed by a micro-Volhard titration described by Eichelberger and Bibler (7). Chloride in the serum was determined by the method of Sendroy (8) using a photoelectric colorimeter.

Sodium was determined by the gravimetric zinc-uranyl-acetate method, in urine as described by Peters and Van Slyke (6) (p. 733), in food and stool by a similar technic after ashing 24 hours at 540° C. in an electric muffle furnace. Serum was prepared for analysis by ashing 24 hours at 490° C. after drying with the addition of sulfuric acid and ferric sulfate as described by Eichelberger (9).

Potassium was determined as the chloroplatinate. Serum and urine dried in silica beakers, the former with the addition of sulfuric acid, were ashed 24 hours at 490° C. The potassium in a suitable aliquot of the ash solution was precipitated and washed by decantation in a 15 cc. centrifuge tube as described by Consolazio and Talbott (10) and the iodoplatinate determined colorimetrically according to Salit (11).

Calcium was determined in urine and food after ashing 24 hours at 540° C. by the method described by Peters and Van Slyke (6) (p. 762) for serum filtrates.



Phosphorus. Inorganic phosphorus was determined in serum and urine by the method of Fiske and Subbarow (12). Food and stool were ashed 24 hours, the former at 450° and the latter at 490° C. and the solution of the ash treated as urine. Very frequent recovery experiments proved the reliability of the method for food and stool.

Nitrogen was determined in urine, food and stool by the boric acid modification of the macro-Kjeldahl method.

The 17-Ketosteroids. For determination of the ketosteroids in the urine of *J. P.* we are indebted to Dr. W. W. Scott of the Department of Urology who used the method of Scott and Vermeulen (13). Dr. R. L. Landau of the Department of Medicine kindly made those of *W. H.*, using the method of Holtorff and Koch (14).

Blood sugar was determined in samples of capillary blood by the method of Miller and Van Slyke (15).

PROTOCOLS

The following observations were made in all five experiments: glucose tolerance, weight balance, water intake, urine volume, and urinary excretion of sodium, chloride, phosphorus and nitrogen.

In this report the individual experiments are designated by the initials of the subject followed by the altitude.

J. P.—11,500 feet. This subject was 28 years old. Control observations were made July 13 to 26, 1942 inclusive. From July 27 to September 6 he was subjected to a simulated altitude of 11,500 feet, six hours a day (9:30 A.M. to 3:30 P.M.), six days a week, for a total of six weeks. Recovery observations were made September 7 to 11. During the whole experiment his body weight remained constant (maximum change

TABLE 5. BALANCE STUDIES. *J.P.—11,500 Feet*

Day[1] of Experiment	Sodium				Chloride			
	Urine g/day	Stool g/day	Food g/day	Balance g/day	Urine g/day	Stool g/day	Food g/day	Balance g/day
1– 3 C	3.25	0.04	3.84	+0.55	5.21	0.05	6.17	+0.91
4– 6	2.90	0.02	3.89	+0.97	4.75	0.04	6.17	+1.38
8–10	3.73	0.02	3.91	+0.16	5.77	0.05	6.29	+0.47
11–13	3.09	0.02	3.90	+0.79	5.01	0.04	6.26	+1.21
1– 3 E	3.62	0.02	3.94	+0.30	5.65	0.04	6.23	+0.54
4– 6	3.46	0.03	3.85	+0.36	5.38	0.06	6.22	+0.78
8–10	3.69	0.01	3.78	+0.08	5.87	0.05	6.13	+0.19
18–20	3.53	0.03	3.93	+0.37	5.77	0.03	6.32	+0.52
25–27	3.34	0.01	3.87	+0.52	5.51	0.02	6.25	+0.72
29–31	3.52	0.03	3.84	+0.29	5.69	0.04	6.19	+0.46
32–34	3.38	0.03	3.90	+0.49	5.50	0.05	6.34	+0.79
36–38	3.53	0.00	3.91	+0.38	5.55	0.01	6.23	+0.67
1– 3 R	3.60	0.02	3.83	+0.21	5.78	0.03	6.26	0.45
	Phosphorus				Nitrogen			
1– 3 C	1.27	0.43	1.99	+0.29	17.6	1.2	21.6	+2.8
4– 6	1.34	0.37	2.01	+0.30	18.2	1.0	21.6	+2.4
8–10	1.33	0.65	1.97	−0.01	18.2	1.6	21.3	+1.5
11–13	1.31	0.64	1.98	+0.03	18.2	1.5	21.4	+1.7
1– 3 E	1.09	0.69	1.96	+0.18	17.8	1.7	21.4	+1.9
4– 6	1.28	0.63	2.00	+0.09	18.1	1.6	21.7	+2.0
8–10	1.25	0.71	1.95	−0.01	18.7	1.6	21.3	+1.0
18–20	1.22	0.58	1.99	+0.19	17.6	1.2	20.5	+1.7
25–27	1.34	0.35	1.95	+0.26	18.5	0.8	19.9	+0.6
29–31	1.36	0.51	2.02	+0.15	17.7	1.3	20.0	+1.0
32–4	1.36	0.71	2.13	+0.06	18.0	1.6	21.3	+1.7
36–38	1.39	0.17	2.07	+0.51	19.2	0.4	19.9	+0.3
1– 3 R	1.45	0.67	2.08	−0.02	19.4	1.4	21.8	+0.6

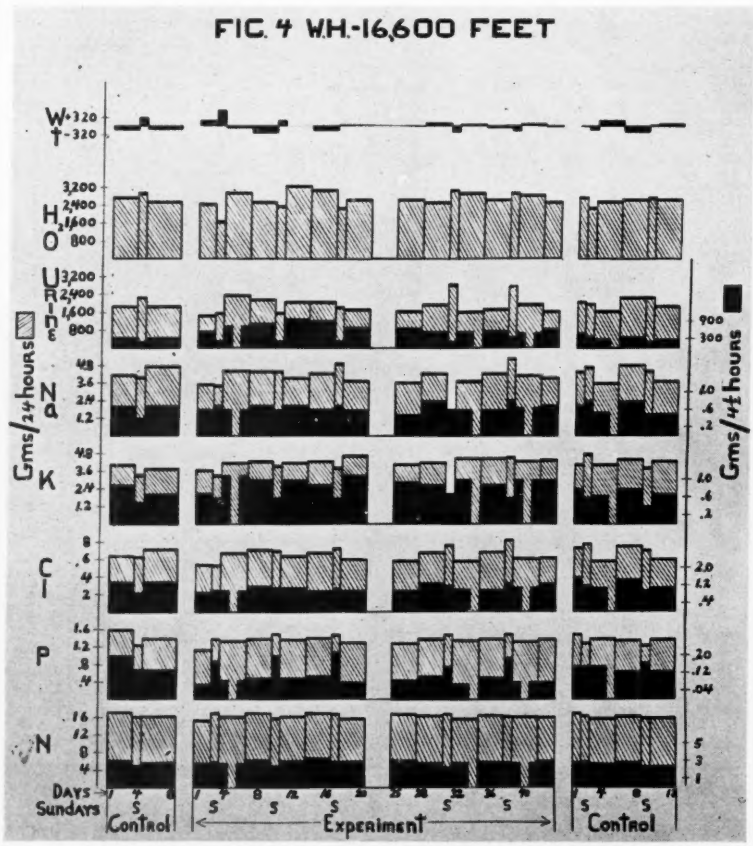
[1] See footnote, Table 2.

0.9 kg.). Urine was collected on a 24-hour basis; analyses for sodium, chloride, phosphorus and nitrogen balances were made, as well as a study of the excretion of 17-ketosteroids.

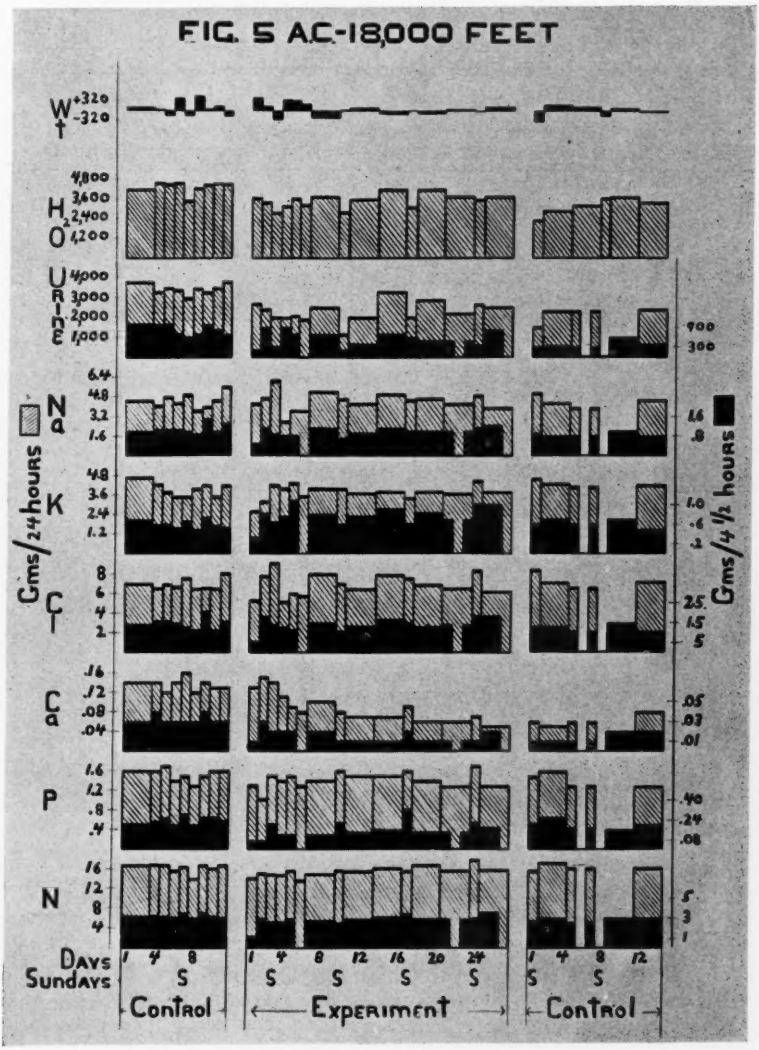
W. H.—11,500 feet. Control observations on this 27-year-old subject were made September 13 to 21, 1942. From September 22 to November 3 he was at a simulated altitude of 11,500 feet, six hours a day (8:00 A.M. to 2:00 P.M.), six days a week for six weeks. Recovery was observed November 4 to 13. His weight remained very constant; he continued his work as a janitor. The urine collections consisted of a fractional specimen of seven hours, including the hours at altitude, and a 24-hour specimen. Studies included, besides those enumerated above, the urinary excretion of potassium, calcium and 17-ketosteroids, and sodium, chloride, phosphorus and nitrogen balances.

R. D.—11,500 feet. This 19-year-old student continued his usual activity during the experiment. Control studies were made November 5 to 22, 1942. From November 23, 1942, to January 4, 1943, he was at a simulated altitude of 11,500 feet, six hours a day (12:00 Noon to 6:00 P.M.), six days a week, for six weeks. The recovery period, January 5 and 6, was shortened by an attack of German measles. *R. D.*'s weight showed a maximum change of 1.6 kg. Urine collections included a five-and-one-half hour collection at altitude and a 24-hour specimen. Potassium excretion was determined in this experiment.

W. H.—16,600 feet. This subject, who was studied also at 11,500 feet, was given a control period (November 19 to 26, 1942) after his recovery from the lower altitude. From November 27, 1942 to January 8, 1943, he was sub-



jected to a simulated altitude of 16,600 feet, four hours a day (8:00 A.M. to 12:00 Noon), six days a week, for six weeks. Recovery studies were made January 9 to 20, 1943. As noted above, his activity was constant, and his three-quarters of his experiment. Control observations were made January 18 to 29, 1943. From January 29 to February 27 he was at a simulated altitude of 18,000 feet, four hours a day (8:00 A.M. to 12:00 Noon), six days a



weight showed an extreme variation of only 1.2 kg. Urine was collected as a four-and-one-half-hour specimen at altitude and a 24-hour specimen. Potassium excretion was determined in this experiment.

A. C.—18,000 feet. This 22-year-old colored subject worked as a janitor during the first week, for four weeks. Recovery observations were made February 28 to March 16, 1943. *A. C.* showed a tendency to gain weight; he had gained 2 kg. by February 4 when his caloric intake was reduced by giving him 25 grams less butter a day. He then maintained a plateau until towards the end of the experiment when

he stopped working and gained 1.1 kg. A four-and-one-half-hour urine collection including the hours at altitude was made, as well as a 24-hour collection. The urinary excretion of potassium and calcium was determined in this case. For eight days before and six days after studies for a few days, or that the completeness of the urine collection was doubted. The data are usually expressed as daily averages for three-day periods except for the values obtained on Sundays when the subjects were not at altitude. Tables 5 and 6 give the sodium,

TABLE 6. BALANCE STUDIES. *W.H.—11,500 Feet*

Day[1] of Experiment	Sodium				Chloride			
	Urine g/day	Stool g/day	Food g/day	Balance g/day	Urine g/day	Stool g/day	Food g/day	Balance g/day
2- 4 C	4.10	0.04	4.65	+0.51	6.37	0.04	7.09	+0.68
5- 6	4.31	0.04	4.57	+0.22	6.62	0.04	7.08	+0.42
1- 2 E	4.52	0.03	4.53	−0.02	6.63	0.04	7.03	+0.36
3- 5	4.79	0.03	4.51	−0.31	7.22	0.04	7.04	−0.22
7- 9	4.19	0.03	4.51	+0.29	6.48	0.04	7.03	+0.51
10–12	3.86	0.03	4.59	+0.70	5.96	0.04	7.09	+1.09
14–16	4.44	0.04	4.61	+0.13	6.85	0.04	7.10	+0.21
17–19	4.36	0.04	4.56	+0.16	6.68	0.04	7.02	+0.30
28–30	4.21	0.03	4.53	+0.29	6.50	0.05	7.06	+0.51
31–33	4.50	0.03	4.47	−0.06	6.94	0.05	6.96	−0.03
35–37	3.64	0.04	4.49	+0.81	5.93	0.04	6.95	+0.98
2- 4 R	4.33	0.04	4.51	+0.14	6.77	0.04	7.04	+0.23
6- 8	4.24	0.04	4.50	+0.22	6.70	0.04	7.05	+0.31
9–10	4.35	0.04	4.55	+0.16	6.76	0.04	7.21	+0.41
	Phosphorus				Nitrogen			
2- 4 C	1.30	0.88	2.41	+0.23	14.6	1.3	19.8	+3.9
5- 6	1.37	0.88	2.27	+0.02	15.7	1.3	19.4	+2.4
1- 2 E	1.24	0.92	2.31	+0.15	15.9	1.3	20.0	+2.8
3- 5	1.33	0.92	2.30	+0.05	16.0	1.3	19.8	+2.5
7- 9	1.36	0.79	2.32	+0.17	15.2	1.3	19.7	+3.2
10–12	1.21	0.79	2.32	+0.32	15.4	1.3	19.8	+3.1
14–16	1.29	0.87	2.24	+0.08	15.7	1.3	19.8	+2.8
17–19	1.36	0.87	2.29	+0.06	16.3	1.3	20.3	+2.7
28–30	1.37	0.85	2.23	+0.01	15.8	1.2	20.9	+3.9
31–33	1.34	0.85	2.33	+0.14	17.1	1.2	20.0	+1.7
35–37	1.29	0.95	2.30	+0.06	16.3	1.4	20.1	+2.4
2- 4 R	1.43	0.93	2.36	0.00	16.8	1.3	20.1	+2.0
6- 8	1.48	0.84	2.36	+0.04	16.4	1.2	19.9	+2.3
9–10	1.46	0.84	2.38	+0.08	16.6	1.2	20.1	+2.3

[1] See footnote, Table 2.

ascent daily excretions were studied to include any immediate effect of altitude which might be masked by a three-day collection.

DISCUSSION OF RESULTS

Figures 1 through 5 present in a detailed manner the results obtained in respect to the weight balance, water intake, urine volume, and the urinary excretion of sodium, potassium chloride, calcium, phosphorus and nitrogen. A break in the figures presenting the metabolic data indicates either that an inulin clearance determination was made, invalidating further chloride, phosphorus and nitrogen balances of two subjects at 11,500 feet, and table 7 gives the serum electrolyte values. Figures 6 and 7 and table 9 present observations on the glucose tolerance.

Urine volume. In the experiment on *W. H.* at *16,600 feet* (fig. 4) a significant increase occurred in the volume of the fractional urine specimens during the first 16 days in the chamber, an effect which diminished somewhat during the rest of the exposure period. To this extent we can support the findings of Armstrong (5) who reported (p. 284) a diuresis during the

TABLE 7. SERUM ELECTROLYTE VALUES

Day[1] of Experiment	Sodium mEq./L.	Potassium mEq./L.	Chloride mEq./L.	Inorganic Phosphate Mg. %
J.P.—11,500 Feet				
9 C	140			
11 C	140			
22 E	136			
31 E	137			
5 R	138			
W.H.—11,500 Feet				
2 C	138		101	
2 E	136		101	
9 E	138		109	
21 E	135		107	
28 E	138		107	
35 E	136		99	
1 R	134		99	
6 R	136			
8 R	140			
R.D.—11,500 Feet				
16 C	141		102	4.3
1 E				3.3
8 E	140	4.3	104	3.6
30 E	140		103	3.7
W.H.—16,600 Feet				
7 C	130	4.7	100	3.4
1 E	140		101	2.3
8 E	140	4.4	102	2.8
41 E	138	4.4	104	2.5
3 R	139	4.9	101	3.3
12 R	137	4.5	99	3.4
A.C.—18,000 Feet				
1 C	140	4.4	98	3.4
4 E	137	4.0	101	1.9
16 R	137		105	3.9

[1] See footnote, Table 2.

hours his subjects were exposed to chronic intermittent anoxia at 12,000 feet. The rest of our data on this point are less striking: *J. P.—11,500 feet* (fig. 1), *W. H.—11,500 feet* (fig. 2) and *R. D.—11,500 feet* (fig. 3) showed a slight and probably insignificant tendency for the fractional and 24-hour urine volumes to be elevated during the first week at altitude; *W.H.—16,600 feet* (fig. 4) showed little if any change in his 24-hour urine volume; and in *A. C.—18,000 feet* (fig. 5) a decrease occurred in both fractional and 24-hour urine volumes at altitude and during recovery.

Water intake. There was no increase in the water intake of *J. P.—11,500 feet* and *W. H.—11,500 feet.* In the other experiments the changes in the water intake were similar to those in the 24-hour urine volume.

Electrolyte excretion. It will be noted in figures 1 to 3 that human subjects at simulated altitudes of 11,500 feet failed to show the spectacular increase in the excretion of sodium, potassium and chloride which others have noted in dogs exposed to 18,000 to 20,000 feet. It is worth recalling, in this connection, that Lewis *et al.* (3) obtained about a two- to three-fold increase in the excretion of sodium, potassium and chloride in dogs exposed twenty-four hours to a simulated altitude of 18,000 feet. Langley and Clarke (4) subjected their normal dog to 20,000 feet, six hours a day, for four days and in the first day the sodium excretion increased about 10-fold and the potassium excretion about five-fold; these effects were lost by the fourth day. In the present experiments with humans at 11,500 feet, on the other hand, the excretion of these electrolytes in both the fractional and 24-hour urine remains, in spite of exposure to altitude, as constant as can be expected, bearing in mind that irregularities in urinary excretion are caused by uncontrollable variations in the water balance (mirrored by our weight-balance data) and in sweating.

TABLE 8. THE EXCRETION OF 17-KETOSTEROIDS

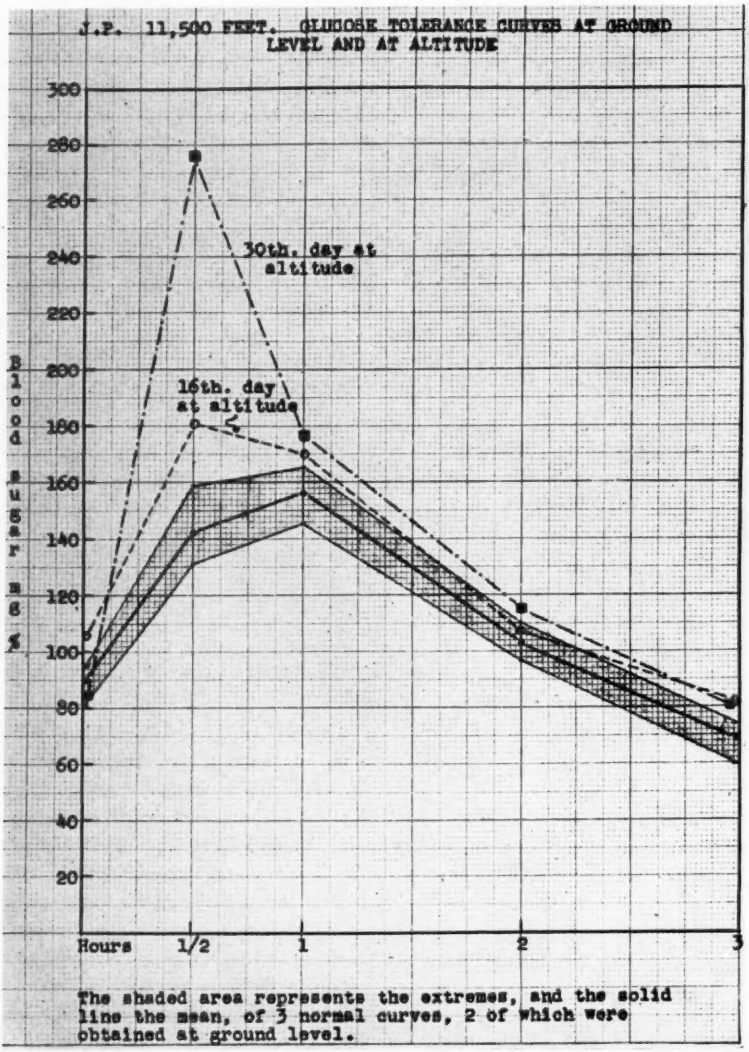
J.P.—11,500 Feet		*W.H.—11,500 Feet*	
Day[1] of Experiment	Ketosteroids Mg./day	Day[1] of Experiment	Ketosteroids Mg./day
4– 6 C	11.3	2– 4 C	22
7 C	13.4	5– 6 C	22
8–10 C	13.8	1– 2 E	21
1– 2 E	12.7	3– 5 E	25
4– 6 E	12.5	7– 9 E	24
8–10 E	*19.0*[2]	10–11 E	20
11 E	11.8	15–18 E	23
22–24 E	15.0	29–31 E	23
25–27 E	9.6	36–38 E	20
36–38 E	9.5	6– 8 R	21
1– 3 R	14.1	9–10 R	20
4 R	11.3		

[1] See footnote, Table 2.
[2] The italicized figure indicates a significant deviation from the control values.

Because of our failure to obtain in three men at 11,500 feet the changes in the excretion of sodium, potassium and chloride which occur in dogs at higher altitudes, experiments with human subjects were performed at simulated alti-

tudes of 16,600 and 18,000 feet. In the latter experiment (18,000 feet) daily excretions were studied for eight days before and six days after the beginning of the experimental period to fractional urine passed at altitude showed a slight and probably not very significant increase in the excretion of potassium, a little more marked in the case of *A. C.—18,000 feet*

FIG 6



bring out any effect which might occur on the first day and be obscured by a three-day collection. In these two experiments, as will be seen in figures 4 and 5, we obtained no significant changes in the fractional or 24-hour excretion of sodium and chloride during exposure. The

than in *W. H.—16,600 feet*. There was no increase in the 24-hour excretion of potassium in either subject.

Since five experiments in four human subjects failed to reveal the significant increase in the excretion of sodium, potassium and chlo-

ride encountered in dogs exposed to anoxia, it is very unlikely that further studies in man would lead to positive results.

The balances of sodium and chloride in *J. P.—11,500 feet* and *W. H.—11,500 feet* (tables 5 and 6) and the serum electrolyte values (table 7) show no significant trends.

TABLE 9. GLUCOSE TOLERANCE

Subject	Altitude	Days	Blood sugar mgm. per cent at				
			0	½	1	2	3 hrs.
J.P.	0	C	95	131	165	97	74
	0	C	93	137	159	102	72
	11,500	4 E	81	159	145	110	60
	11,500	16 E	*106*[1]	*181*	170	107	82
	11,500	30 E	85	*276*	177	115	81
	0	5 R	86	167	*113*	96	68
W.H.	0	C	92	185	163	66	81
	0	C	96	181	152	92	87
	11,500	8 E	*111*	179	166	96	*111*
	11,500	17 E	96	182	142	87	71
	11,500	25 E	91	176	145	70	81
	11,500	29 E	90	169	144	83	82
	11,500	38 E	88	151	127	67	74
	0	9 R	89	161	144	68	75
R.D.	0	C	85	175	131	94	85
	0	C	84	158	186	133	77
	11,500	3 E	83	161	*115*	139	*118*
	11,500	10 E	96	146	129	*184*	*158*
	11,500	19 E	81	143	141	102	82
	11,500	24 E	90	125	148	97	72
	11,500	31 E	77	172	166	120	79
	11,500	41 E	87	150	140	94	76
W.H.	0	C	92	185	163	66	81
	0	C	96	181	152	92	87
	0	C[2]	89	161	144	68	75
	16,600	5 E	88	152	122	91	75
	16,600	12 E	88	170	157	85	81
	16,600	21 E	85	165	152	52	79
	16,600	34 E	88	160	129	83	78
	16,600	40 E	91	154	*118*	81	79
	0	5 R	96	154	131	68	89
A.C.	0	C	87	159	140	92	71
	0	C	78	160	158	90	53
	18,000	6 E	83	148	134	106	83
	18,000	22 E	85	148	141	81	75
	18,000	27 E	92	146	131	87	79
	0	6 R	86	125	144	67	75

[1] Italicized figures are those which differ significantly from control values for the same period.

[2] This test was performed 9 days after exposure to 11,500 feet and 15 days before exposure to 16,600 feet.

Phosphorus and calcium excretion. While there is no change in the 24-hour urinary excretion of inorganic phosphorus (figures 1–5), a significant and consistent decrease occurs in the phosphorus content of the fractional urine specimens passed at altitude. Usually on Sundays, when the subject was not in the chamber, the fractional excretion of phosphorus was increased. That anoxia in the human (unlike the dog) leads to a *decreased* excretion of phosphorus in the urine has already been noticed by Lewis and co-workers (3) in acute experiments and Sundstroem (16) in chronic observations at Leadville and Pike's Peak. The explanation of this effect is not clear, as is indicated by the following facts. First, the serum inorganic phosphorus values tend to be lower at altitude (table 7), while the phosphorus balance of two of our subjects was not changed (tables 5 and 6). Second, as noted below, the changes in the phosphorus excretion were not accompanied by like changes in the output of nitrogen. Finally, the urinary excretion of calcium was studied in two subjects, *W. H.—11,500 feet* and *A. C.—18,000 feet* (figures 3 and 5), with the finding that the calcium and phosphorus excretions showed a similar trend only in the case of the fractional urines of *A. C.—18,000 feet*. The 24-hour output of calcium in both cases and the excretion in the fractional urine of *W. H.—11,500 feet* tended to drop during the course of the study in a manner quite unlike the behavior of the phosphorus.

Nitrogen excretion. The excretion of nitrogen in both the fractional and the 24-hour urine was unchanged by exposure to altitude (figures 1–5). The nitrogen balances given in tables 5 and 6 show in *J. P.—11,500 feet* and *W. H.—11,500 feet* a retention of nitrogen of approximately 2 grams a day throughout the experiment and the data for the other experiments, though not as complete, suggest a similar finding. This retention is probably due to the superior quality of the experimental diet as compared with the subjects' previous fare.

The 17-ketosteroids. The excretion of 17-ketosteroids by *J. P.—11,500 feet* and *W. H.—11,500 feet* is shown in table 8, where it will be noted that while there were no changes in *W. H.*, *J. P.* showed a definitely increased excretion on the eighth to tenth experimental day.

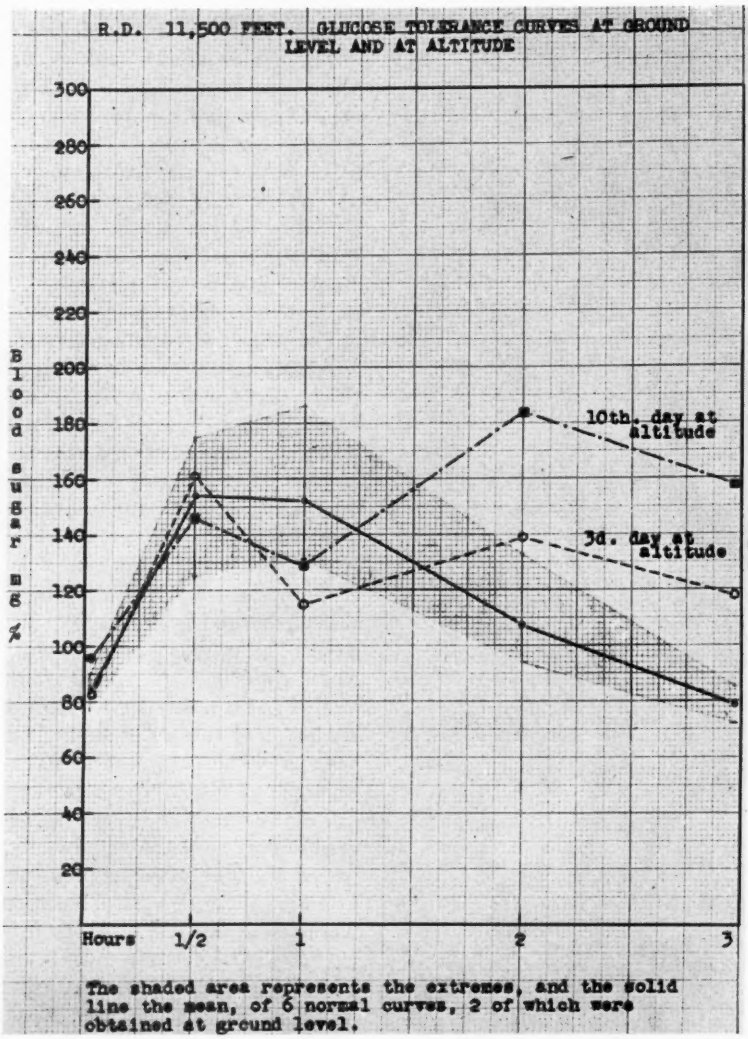
Glucose tolerance. In the three subjects studied at 11,500 feet, moderate but definite abnormalities were noted in the behavior of the blood sugar, principally in the direction of a decreased tolerance for glucose (table 9 and figures 6 and 7). *J. P.* during exposure showed an elevation of the fasting blood sugar on one oc-

casion and of the peak value at one-half hour on two occasions, while in the test after exposure the one-hour value was unusually low. In *W. H.* one of the tests at altitude showed high values for the fasting and three-hour specimens. In *R. D.*, in two tests made during exposure, the blood sugar remained distinctly high in the latter part of the curves.

The two subjects studied at 16,600 and 18,000 feet showed no alteration in glucose tolerance except for one low value at the one-hour period in *W. H.*

The mechanism by which the observed changes in blood sugar were produced is not clear from the data at hand. Their failure to appear at the higher altitudes indicates that the degree of anoxia is not a factor and, since at the lower altitude they occurred early during the experimental period in two of the cases and late in the third, it cannot be stated that dimi-

FIG. 7



nution of tolerance is proportional to the duration of exposure. There is no indication of adrenal-cortical stimulation as judged by the excretion of electrolytes or nitrogen, and while the 17-ketosteroid excretion was increased from the eighth to the tenth day at altitude in the case of *J. P.*, there was no such increase at the time when tolerance for glucose was diminished. Moreover, *W. H.* showed no rise in urinary ketosteroids at any time. No hyperactivity of the thyroid occurred as indicated by repeated determinations of the basal metabolism. The serum bilirubin and the colloidal-gold test gave no suggestion of hepatic disturbance. It must be recognized, of course, that alterations in endocrine function may have occurred without being detected by the methods used. We have no evidence bearing on the pituitary and none implicating the pancreas other than the decreased tolerance itself. There is some evidence from other sources, as suggested by Langley and Clarke (4), that lowered CO_2 tension of the serum may influence carbohydrate metabolism. Lewis *et al.* (3), for example, found that the increase of liver glycogen observed in animals exposed to anoxia could be diminished by the administration of CO_2. Conversely, the studies of Polonovski (17) in humans, although less convincing, suggest that the ingestion of carbohydrate minimizes the disturbance in both acid-base balance and blood-sugar levels produced by anoxia. So far as the present experiments are concerned, it can only be stated that there was no correlation between the values for CO_2 and the time of appearance or disappearance of the abnormalities in blood-sugar behavior.

The decreased tolerance for glucose observed in these investigations is in contrast to the increased tolerance in two acclimatized subjects at 17,500 feet reported by Forbes. (18)

SUMMARY

Studies were undertaken in an effort to discover whether chronic anoxia produces in man the metabolic changes which in animals have suggested stimulation of the adrenal cortex. Five experiments were performed on four human subjects, 19 to 28 years of age, at altitude pressures of 11,500, 16,600 and 18,000 feet. Exposure was from four to six hours, six days a week, for from four to six weeks. The subjects were on constant, weighed diets and careful, metabolic technic was followed throughout.

In only one experiment (16,600 feet) was there any significant increase in the volume of urine secreted at altitude and this diminished somewhat after the sixteenth day of exposure. It was not accompanied by an increased fluid intake.

In three subjects at 11,500 feet, the urine passed at altitude as well as the 24-hour specimens showed no change in the content of sodium, chloride or potassium. Experiments at 16,600 and 18,000 feet likewise showed no change in excretion of sodium or chloride but a slight increase in the excretion of potassium during the hours of exposure.

The excretion of phosphorus was definitely decreased in the urine passed at altitude. This change was not reflected in the 24-hour urine samples. Urinary calcium was found to decrease during exposure in both the fractional and the 24-hour specimens but in a manner unrelated to the phosphorus excretion.

Nitrogen excretion was unchanged from control values in all experiments.

The 17-ketosteroid excretion studied in two subjects at 11,500 feet showed no change except for a transient but well marked increase in one subject for the eighth to tenth experimental days.

Glucose tolerance was moderately decreased in two subjects and slightly in one subject in one or more tests made at 11,500 feet. This was not observed in the experiments at 16,600 or 18,000 feet.

CONCLUSION

With the possible exceptions of a slight increase in potassium excretion in two subjects, a transient rise in 17-ketosteroid excretion in one subject and a moderate decrease in tolerance for glucose in two, the observations here reported provide no evidence that the human adrenal cortex is influenced by chronic intermittent anoxia.

ADDENDUM

Since the preparation of this paper, Pincus and Hoagland (J. Aviation Med. 14: 173, 1943) have published studies on the 17-ketosteroid excretion in subjects under stress, with and without anoxia. They have

shown that the effort incident to a long-continued, complicated psychomotor test involving great concentration produces an increase in the 17-ketosteroid excretion as compared with resting control values and that this increase is markedly augmented when the same test is performed under conditions of anoxia. These results are of great interest but they are not incompatible with our finding of only a questionable increase in the excretion of these substances during anoxia in *resting* subjects. It might be that further studies of anoxic human beings under stress would reveal other evidence of altered adrenal function, such as increased excretion of electrolytes, etc., but it still remains a curious fact that animals show such changes even though at rest, while man, under the same conditions, does not.

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Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNE FORBES, ROBERT B. GREENBLATT, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, THOMAS H. MCGAVACK, A. E. MEYER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, AND HAROLD WOOSTER.

ADRENALS

INGLE, D. J., G. B. GINTHER AND J. NEZAMIS

Effect of diet in rats on adrenal weights and on survival following adrenalectomy. *Endocrinol.*, 32: 410. 1943.

A study was made of the effect of different proportions of carbohydrate, protein and fat in diet on the weights of adrenal glands of rats and on the periods of survival following adrenalectomy. The observed differences were small and probably without significance.—*Author's Summary.*

MACFARLAND, W. E.

Adrenal cortical function independent of direct nervous action. *J. Exper. Zool.*, 95: 345. 1944.

Adrenal innervation, with especial reference to the cortex, was studied in 75 mature albino rats. In 10 animals, Wallerian degeneration within the gland, following excision of the greater and lesser splanchnic nerves, produced marked changes in the medulla but with no detectable cytological changes in the glandular parenchyma of the cortex. Autoplastic transplantation of the left adrenal to the subcutaneous fascia of the left inguinal region was performed in 48 animals. In 24 of these, 8 transplants were recovered from 29 to 64 days later as small nodules of cortical tissue. The right adrenals had hypertrophied and had maintained the animals in good condition. In the other 24 rats of this group, transplantation was followed in 5 to 307 days by removal of the right adrenal. Fifteen of these animals died from 1 to 15 days after the operation and 9 survived to submit to a third operation involving removal of the transplants from 6 to 42 days after loss of the right adrenal. Death with symptoms of adrenal cortical insufficiency was the common result from 1 to 36 days later. The functional activity of the transplants was shown primarily by their life-preserving capabilities. Valuable evidence was also obtained by a study of weight changes in the animals following each operation supplemented by a microscopic check on serial sections of each graft. Survival capacity of the stock, from which the transplantation series was chosen, was checked by bilateral adrenalectomy of 6 animals in 1-stage operations. Death occurred from 1 to 17 days. Microscopic examination of serial sections of 25 normal adrenals showed the nerve supply entering the gland as a few small bundles and scattered fibers; these passed without branching, through the cortex and terminated in the medulla. A similar examination of the transplants showed them to be, in cases where physiological evidence for function was strongest, robust masses of cortical tissue. Their cytology was apparently normal, but they lacked a medulla or any detectable nerve content. Regeneration was most effective when (a) the whole adrenal was transplanted and (b) the right adrenal was left in situ for a period not exceeding 10 days before removal. Approximately 60% of the glands transplanted in toto to the groin showed signs of functional regeneration. Accessory cortical nodules were found in 25% of serially sectioned rat adrenals. Ganglion cells were never found in the cortex but were found in the medulla in about 50% of all adrenals examined. There was some evidence that ganglion cells were more abundant in the right than in the left adrenal. All the anatomical and physiological evidence gained from a study of normal, denervated and transplanted adrenals in the albino rat points to the conclusion that the medulla of this gland is the only part which is innervated by secretory fibers and that the cortex has no direct neural control of its functional activity.—*Author's Summary (Edited).*

POTTER, H. W., AND L. H. BRONSTEIN.

The Waterhouse-Friderichsen syndrome. *J. Lab. & Clin. Med.*, 29: 703. 1944.

Two patients with the Waterhouse-Friderichsen syndrome have been seen among more than 80 cases of meningococcus meningitis. The first

of these whose record is briefly summarized by the authors died 20 hours after admission to the hospital and 44 hours after the onset of symptoms. Following hospitalization, he received adequate sulfonamide therapy on which he improved until shortly before death. Post-mortem examination revealed the classical findings of the syndrome mentioned.

The second patient, a soldier whose age is not stated, was taken acutely ill some eight hours before admission to the hospital. The outstanding findings were a confused mental state, widespread purpuric eruption, a blood pressure of 60/40, and a positive blood culture for the meningococcus. The spinal fluid was clear, showed two lymphocytes per cu. mm., gave negative tests for globulin, revealed no organism on smear or in culture, and contained 77 mgm. of sugar per 100 cc. There was a mild leucocytosis and an azotemia of moderately severe degree. His treatment included the use of sulfadiazine, watery extract of the adrenal cortex, desoxycorticosterone acetate, salt tablets, and blood plasma. An initial dose of 4 gr. of sulfadiazine on admission was followed by 2 gr. at four-hour intervals, to a total of 69 gr. during his hospitalization. Ten cc. of adrenal cortex extract was given intravenously two hours after admission and repeated daily for three days. Approximately 5 mgm. of desoxycorticosterone acetate was administered intramuscularly daily for each of the first three days of hospitalization, the initial dose being given 10 hours after admission. A venoclysis of 500 cc. of blood plasma was made between the tenth and twelfth hours after admission to the hospital. Ten subsequent infusions of 250 cc. each were given at approximately six hourly intervals, three on the second, four on the third, and three on the fourth day of hospitalization. On the fourth day after admission the patient was apparently out of danger with normal temperature, pulse, and respirations, and a blood pressure of 102/70. Three months after recovery, adrenocortical function was normal as tested by by the Cutler-Power-Wilder procedure. The authors believe the early recognition of the condition and prompt institution of therapy were responsible for recovery. They were of the opinion that the patient obtained more benefit from the blood plasma than from the adrenocortical therapy, although they suggest that they may not have used the latter in sufficiently large doses. Parenthetically, it may be said that they employed as much adreno-cortical therapy as has been used in the majority of cases with recovery and in which no use whatsoever was made of blood plasma, but in the majority of which salt was made available in a readily assimilable form. —*T.H.McG.*

SAMUELS, L. T., G. T. EVANS AND J. L. MCKELVEY

Ovarian and placental function in Addison's disease. *Endocrinol.*, 32: 422. 1943.

In 2 non-pregnant women suffering from Addison's disease the estrogen excretion, while low, showed the normal double peak; sodium pregnanediol glucuronidate appeared during the latter half of the cycle. Since the amount of functioning adrenal cortex in severe Addison's disease is very small, and since in these cases the 17-ketosteroid excretion indicated that cortical function was very low, it is concluded that ovarian function cannot to any major degree be dependent upon a correlated rhythm in the adrenal cortex. As long as electrolyte balance is maintained the pituitary may, therefore, carry on the normal periodic production of gonadotropic hormones in the absence of adrenal cortex hormone to maintain life without salt therapy. In one case of Addison's disease studied during pregnancy, the excretion of estrogen and sodium pregnanediol glucuronidate showed the smooth progressive increase characteristic of normal pregnancy. The excretion of thse compounds began to drop just before parturition and returned to normal non-pregnant levels thereafter. The excretion of 17-ketosteroids in the pregnant woman remained very low until the sixth month of pregnancy and then rose to a level of 11 to 15 mg. per day. It immediately fell to the original low level after birth of the child. Just before parturition the proportion of 'free' 17-ketosteroids increased from a level of approximately 20 per cent to 50 per cent of the total but returned to the original 20 per cent within a week after childbirth. It is concluded from these studies that the ovary and placenta undergo their normal rhythm and can produce their normal secretory products in severe Addison's disease as long as the individual is maintained in good general metabolic condition by appropriate therapy.—*Author's Summary.*

SCHNEIDER, R. W.

An appraisal of the water test of adrenal function. *Clev. Clinic Quarterly*, 11: 22. 1944.

The water excretion test for adrenal function, as originally described by Robinson, Power and Kepler was used in 173 cases to determine its value in the diagnosis and exclusion of adrenal insufficiency. The author discusses the advantage and disadvantage of its use and indicates in a case summary the various clinical conditions

which may give a false positive result.—*R.St.J.*

SHIPLEY, R. A.

Treatment of Addison's disease with pellets of desoxycorticosterone acetate. *Am. J. M. Sc.*, 207: 19. 1944.

Pellets of DCA maintained 5 of 7 patients with Addison's disease for periods of 7 to 40 months. These patients were able to carry on work involving moderate physical activity. Such treatment, however, failed to restore normal carbohydrate metabolism, and such patients may easily be made hypoglycemic by fasting. When infection is present additional hormone is needed, and cortical extract should be given. The absorption rate is fairly constant in different patients. The average number of 75 mg. pellets required to be implanted initially is 4 to 6 and the effective life of each pellet is 9 to 10 months.—*Courtesy Biol. Absts.*

TEPPERMAN, J., F. L. ENGEL AND C. N. H. LONG

Effect of high protein diets on size and activity of the adrenal cortex in the albino rat. *Endocrinol.*, 32: 403. 1943.

Studies have been made of the effect of variations in the protein and carbohydrate content of the diet on the adrenal size of albino rats. Animals fed raw ground beef (55% protein) or a 78 per cent casein diet for 4 to 7 weeks showed a 40 to 50 per cent increase in adrenal size when compared to control rats fed Purina fox chow (24.4% protein, 61% carbohydrate). Hypertrophy of the enucleated glands of rats on a high protein diet demonstrated that the enlargement was primarily cortical. A similar degree of hypertrophy was observed after the feeding of a diet containing 60 per cent casein and 20 per cent carbohydrate demonstrating that the low carbohydrate content of the previous diets probably was not the cause of the enlargement. The cortical cells of the enlarged glands showed lipoid depletion on histologic examination. Saline extract of the anterior pituitary greatly increased the gland size of both chow and meat-fed animals over that achieved by diet alone. Examination of the carbohydrate levels in the two groups revealed elevations of the fasting blood sugar and liver glycogen in the meat-fed rats comparable to that seen after administration of potent cortical extracts. There were no significant differences in the oxygen consumption or blood keto- and amino-acid levels in the two groups. The rats fed the high protein diet exhibited a striking rise in blood sugar after the parenteral administration of amino acids, but this effect was abolished by adreno-demedullation. On the basis of the survey of the literature and the experimental data on animals receiving high protein diets it is suggested that some event or series of events occurring during the catabolism of protein may serve as a simulus for the hypertrophy of the adrenal cortex observed in a variety of circumstances.—*Author's Summary.*

TEPPERMAN, J., F. L. ENGEL AND C. N. H. LONG

A review of adrenal cortical hypertrophy. *Endocrinol.*, 32: 373. 1943.

ENDOCRINE GENERAL

BANCROFT, I. R.

Hormones and the skin. *California and West. Med.*, 61: 60. 1944.

A careful and critical review of relationship of pituitary, thyroid and sex hormones to skin physiology and functions. Author is of the opinion that while there is some evidence that sex hormones retard degenerative changes in the skin, rejuvenation by means of estrogenic or androgenic hormone therapy has not been successful. It is believed that heredity factors limit the extent of hormone activity.—*D.A.M.*

FINKLER, RITA S., AND GEORGE M. COHN

Hormonal effects on growth in children. *Arch. Pediat.*, 60: 362–379. 1943.

Growth observations were made on 125 children treated with various hormone preparations. Of 24 children treated with thyroid extract 14 showed appreciable growth acceleration and 10 did not exceed the normal growth expectation. Five of 21 children treated with anterior growth extract showed a moderate growth acceleration, 4 showed a slight growth acceleration and 12 failed to show any increase in growth rate. Of 59 children treated with chorionic gonadotropin, 37 showed an increase in growth rate, 18 maintained the original rate of growth and 4 showed a decrease. Seventeen of 21 children who received testosterone propionate showed an accelerated rate of growth and 4 maintained their original rate of growth.—*Courtesy Child Development Abstracts.*

HILL, B. R., AND B. B. LONGWELL

Urinary steroids from breast cancer patients. *Endocrinol.*, 32: 319. 1943.

The urine of post-menopausal women with cancer of the breast, or with metastatic growths

from this origin, was examined for its steroid content. Androsterone, 3-α-hydroxy-etiocholanone-17, an impure form of pregnanediol, cholesterol and a low melting hydrocarbon were isolated. Comparison of these results with those of other workers who have examined the urine of ovariectomized women, of normal women, or of cancerous men and women shows that our findings do not constitute positive evidence that the compounds isolated bear a relationship to the existence of malignant growths.—*Author's Summary.*

LI, C. H., H. M. EVANS AND M. E. SIMPSON

Adrenocorticotropic hormone. *J. Biol. Chem.*, 149: 413. 1943.

A method is described for the isolation of pure adrenocorticotropic hormone from pituitary tissue (sheep). The electrophoretic, sedimentation, and solubility data meet the essential criteria for a single substance. Biologic tests indicated the hormone to be free of other anterior hypophyseal hormones. The molecular weight is approximately 20,000 and the isoelectric point about 4.7. The hormone was stable at 100° in buffer of pH 7.5 and in 0.1M HCl solutions, but not in 0.1M NaOH. Its adrenocorticotropic activity was destroyed by trichloracetic acid and by tryptic digestion, but it had marked stability to peptic digestion.—*C.W.H.*

MARX, W., M. E. SIMPSON AND H. M. EVANS

Purification of the growth hormone of the anterior pituitary. *J. Biol. Chem.*, 147: 77. 1943.

A method is described for the purification of growth hormone from beef hypophyses. The final product contained approximately 130 growth units (hypophysectomized rat) per mg. It contained less than 0.05 per cent of follicle-stimulating hormone, less than 0.1 per cent of interstitial cell-stimulating hormone, less than 0.3 per cent of thyrotropic hormone, less than 0.5 per cent of lactogenic hormone, and less than 0.5 per cent of andrenocorticotropic hormone. The product had the properties of a protein, probably a globulin. Electrophoretic measurements in the Tiselius apparatus show the preparation to consist of two components.—*C.W.H.*

SAYERS, G., A. WHITE AND C. N. H. LONG

Preparation and properties of pituitary adrenotropic hormone. *J. Biol. Chem.*, 149: 425. 1943.

A method is described for the preparation of pure adrenotropic hormone from pituitary tissue. The product had the properties of a protein and behaved as a single component in the Tiselius apparatus and in the ultracentrifuge. The isoelectric point, as determined by electrophoresis, was between 4.7 and 4.8. The sedimentation constant indicates the molecular weight to be approximately 20,000. A total dose of 5 mg. of the hormone completely restored adrenal weights in rats 10 days after hypophysectomy. A daily dose of 25 μg. maintained adrenal size and function in rats when started the first day after hypophysectomy. Five μg. daily produced adrenal-stimulating effects, while 2 μg. were without effect. The adrenotropic hormone preparation exhibited none of the activities of the growth, gonadotropic, thyrotropic, or lactogenic hormones. This product was obtained from hog hypophyses. Highly purified fractions of adrenotropic hormone have been obtained from bovine and sheep hypophyses; these preparations are apparently similar to, if not identical with, the product from hog glands.—*C.W.H.*

SCHNEIDER, R. W., AND E. PERRY MCCULLAGH

Infantalism, congenital webbed neck and cubitus valgus. (Turner's Syndrome) *Clev. Clinic Quarterly*, 10: 112. 1943.

Seven cases are reported, in which the genital hypoplasia, primary amenorrhea, delayed development of secondary sexual characteristics and congenital defects such as webbed neck are consistent with Turner's syndrome. The cases are discussed with particular reference to the distinguishing features between Turner's syndrome and pituitary infantilism.—*R.St.J.*

SCHUMAN, W.

The possible significance of vaginal smears in the diagnosis of certain disturbances of pregnancy. *Am. J. Obst. and Gynec.*, 47: 808. 1944.

Vaginal smears were taken in approximately 350 patients representing all stages of pregnancy. The author believes pregnancy might be diagnosed on the basis of a pronounced degree of cornification. The highest degree of cornification was seen in a case of hyperemesis and a definitely increased amount of cornification was noted in a patient with early hypertensive toxemia. In an instance of missed abortion, fresh cornification was not present. Pus is not considered a normal component of the vaginal smear of normal pregnancy.—*E.C.H.*